Request Jan Delcotto 86859

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Jennifer Kim Examiner #: 77469 Date: 2/14/03
Art Unit: 1617 Phone Number 30 8-2232 Serial Number: 10/088,113
Mail Box and Bldg/Room Location: 2B17 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Medicament for treatment of neuropathies

Inventors (please provide full names): Juerg Lakeida

Earliest Priority Filing Date: 10/12/1999

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

1) Please search Claims 1, 2 + 3.

2) Please provide registry # for cpd. III in claim 3.

3) Please separate & label the search of compound I and Ia)

THX,

JMK

Art Special Reference Librarian Biotechnology & Chemical Library

****

STAFF USE ONLY

Searcher: _____
Searcher Phone #: _____
Searcher Location: _____
Date Searcher Picked Up: 2/19/03
Date Completed: 2/26/03
Searcher Prep & Review Time: _____
Clerical Prep Time: _____
Online Time: 1.50

Type of Search

NA Sequence (#) _____
AA Sequence (#) _____
Structure (#) _____
Bibliographic _____
Litigation _____
Fulltext _____
Patent Family _____
Other _____

Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
Dr.Link _____
Lexis/Nexis _____
Sequence Systems _____
WWW/Internet _____
Other (specify) _____

PTO-1590 (8-01)

L11 ANSWER 4 OF 111 USPATFULL
AB The present invention provides aminoalkoxy carbazole derivatives, and more specifically, provides compounds of formula (I) ##STR1##

wherein R.sub.1, R.sub.2, R.sub.3, R.sub.4, R.sub.8 and R.sub.9 are described herein. These compounds are 5-HT ligands, and are useful for treating diseases wherein modulation of 5-HT activity is desired.

AN 2003:33477 USPATFULL
TI Aminoalkoxy carbazoles for the treatment of cns diseases
IN TenBrink, Ruth Elizabeth, Kalamazoo, MI, United States
PA Pharmacia & Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)
PI US 6514968 B1 20030204
AI US 2000-652768 20000831 (9)
PRAI US 1999-152638P 19990907 (60)
US 2000-203771P 20000512 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: McKane, Joseph K.; Assistant Examiner: Wright, Sonya N.
LREP Engelmann, John H.
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 3405
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Aminoalkoxy carbazoles for the treatment of cns diseases
SUMM Many diseases of the **central nervous system** are influenced by the adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example, serotonin has been implicated in a number of diseases and conditions which originate in the **central nervous system**. These include diseases and conditions related to sleeping, eating, perceiving pain, controlling body temperature, controlling blood pressure, depression, anxiety, schizophrenia,. . .
SUMM . . . these studies and observations suggest that compounds that antagonize the 5-HT receptor will be useful in treating disorders of the **central nervous system**.
SUMM a method of treating or preventing diseases or disorders of the **central nervous system** such as: psychosis, paraphrenia, psychotic depression, mania, schizophrenia, schizophreniform disorders, schizoaffective disorder, delusional disorder, panic disorder, a phobia, obsessive compulsive. . . somatoform disorders, an inhalation disorder, an intoxication disorder, movement disorder (e.g., Huntington's disease or Tardive Dyskinesia), oppositional defiant disorder, peripheral **neuropathy**, post-traumatic stress disorder, premenstrual dysphoric disorder, a psychotic disorder (brief and long duration disorders, psychotic disorder due to medical condition,. . .
SUMM . . . a pharmaceutically acceptable salt thereof for use in medical diagnosis or therapy (e.g. the treatment or prevention of 5-HT related **central nervous system** diseases or disorders),
SUMM . . . compound of formula (I) or a pharmaceutically acceptable salt thereof to prepare a medicament for treating or preventing 5-HT related **central nervous system** diseases or disorders such as anxiety, obesity, depression, schizophrenia, a stress related disease (e.g. general anxiety disorder), panic disorder, a. . .
CLM What is claimed is:
. . . and other somatoform disorders, an inhalation disorder, an intoxication disorder, movement disorder, Huntington's Disease, Tardive Dyskinesia, oppositional defiant disorder, peripheral **neuropathy**, post-traumatic stress disorder, premenstrual dysphoric disorder, a

2000049125 EMBASE

TI **Current** and emerging treatments for the **diabetic neuropathies**.

AU Boulton A.J.M.

CS Prof A.J.M. Boulton, Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, United Kingdom.
ajmb@fs1.cmht.nwest.nhs.uk

SO Diabetes Reviews, (1999) 7/4 (379-386).
Refs: 84
ISSN: 1066-9442 CODEN: DBRVEO

CY United States

DT Journal; General Review

FS 003 Endocrinology
006 Internal Medicine
008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles

LA English

SL English

AB This review focuses on the therapeutic approach to patients with symptomatic diabetic neuropathies. Diabetic neuropathy is a diagnosis that requires exclusion of other causes; there are no diagnostic tests that confirm that the symptoms and signs are definitely a result of diabetes. For those patients with painful or paresthetic symptoms, optimal stable glycemic control should be the first aim, remembering that insulin is not always required in type 2 diabetes. The tricyclic drugs, usually amitriptyline or imipramine, remain the first-line drug therapy for painful symptoms. Their efficacy has been confirmed in several controlled trials. Of the newer agents, the anticonvulsant gabapentin seems to offer many of the benefits of the tricyclic agents without the troublesome side effects, and the centrally acting drug tramadol has proven efficacy for short-term treatment. Topical or nonpharmacologic treatments may help in some cases; some data support the use of topical capsaicin, and longterm open trials suggest a possible benefit of acupuncture. Of new agents that may modify pathogenetic mechanisms leading to neuropathy, the antioxidant .alpha.-lipoic acid shows promise from a number of controlled studies. The results of multinational multicenter trials of this agent and newer, potent aldose reductase inhibitors are awaited with interest. Recent developments in autonomic neuropathy include the arrival of sildenafil, which appears to help up to 60 of patients with erectile dysfunction. Topical glycopyrrolate is another new therapy for autonomic dysfunction; in a randomized trial, it was confirmed to markedly reduce gustatory sweating. Finally, whereas < 20 of neuropathic patients experience symptoms, all neuropathic patients are at potential risk of insensitive foot ulceration and require education in preventive foot care, regular podiatry, and frequent follow-up, always inspecting the feet.

CT Medical Descriptors:

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 17:59:54 ON 26 FEB 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   25 FEB 2003  HIGHEST RN 494824-56-5
DICTIONARY FILE UPDATES:  25 FEB 2003  HIGHEST RN 494824-56-5

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can 17

L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   139755-83-2  REGISTRY
CN   Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-
     d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   1H-Pyrazolo[4,3-d]pyrimidine, piperazine deriv.
OTHER NAMES:
CN   5-[2-Ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-
     1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
CN   Sildenafil
FS   3D CONCORD
MF   C22 H30 N6 O4 S
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN,
       CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
       IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPAT2,
       USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:   WHO
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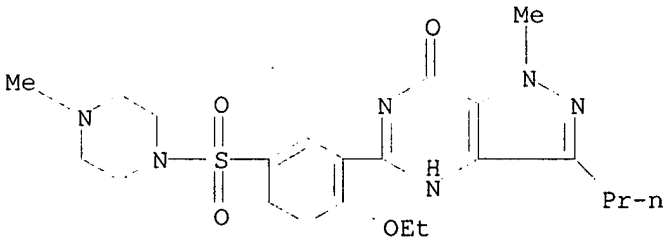

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

374 REFERENCES IN FILE CA (1962 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
377 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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REFERENCE 2: 138:83422

REFERENCE 3: 138:83148

REFERENCE 4: 138:82919

REFERENCE 5: 138:66667

REFERENCE 6: 138:66615

REFERENCE 7: 138:66512

REFERENCE 8: 138:66430

REFERENCE 9: 138:55978

REFERENCE 10: 138:49845

=> s l8 and viagra
1 VIAGRA
L83 1 L8 AND VIAGRA

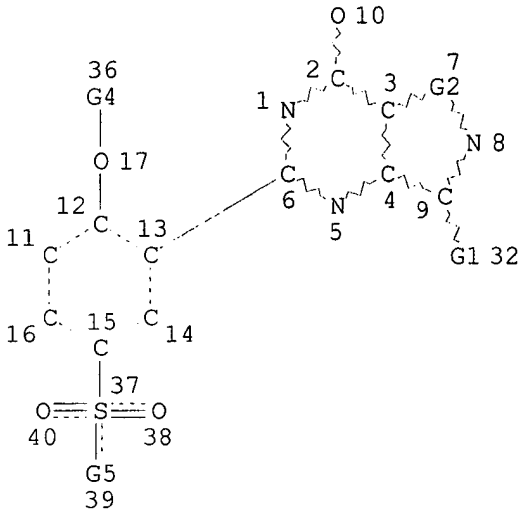
=> d ide can

L83 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 171599-83-0 REGISTRY
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)
CN Sildenafil citrate
CN UK 92480-10
CN **Viagra**
MF C22 H30 N6 O4 S . C6 H8 O7
CI COM
SR CAS Registry Services
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS, CBNB, CEN, CHEMCATS, CIN, DIOGENES, DRUGPAT, DRUGUPDATES, IPA, MRCK*, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S

Page 1-A



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VAR G5=NH2/41/43/52/47/49
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DEFAULT ECLEVEL IS LIMITED
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ECOUNT IS M1 N AT 52

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NUMBER OF NODES IS 50

STEREO ATTRIBUTES: NONE

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L21	82	SEA FILE=REGISTRY ABB=ON PLU=ON L15 AND NC2NC2/ES
L22	50	SEA FILE=REGISTRY ABB=ON PLU=ON L21 NOT (L19 OR L7 OR L8)
L23	42	SEA FILE=REGISTRY ABB=ON PLU=ON L22 AND S/ELS
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L25	4	SEA FILE=REGISTRY ABB=ON PLU=ON L24 AND (C24H34N6O5S OR C24H32N6O5S OR C22H30N6O5S OR C21H28N6O5S)
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L31	6	SEA FILE=REGISTRY ABB=ON PLU=ON (L28 OR L30)
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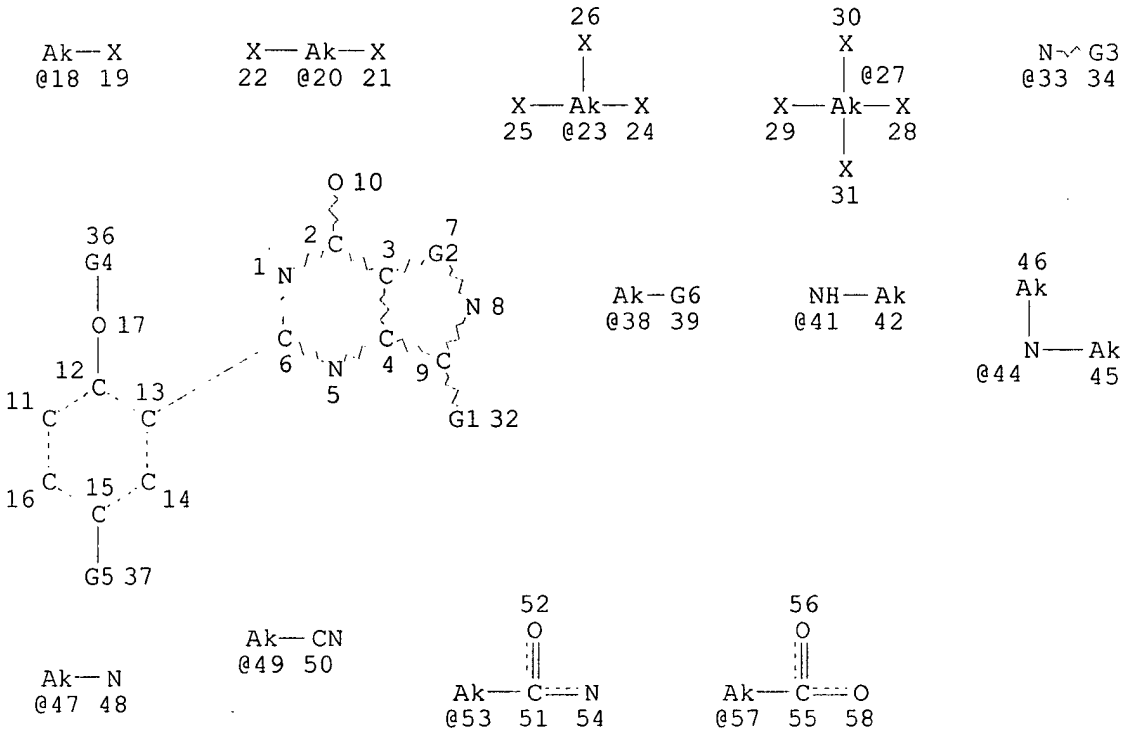

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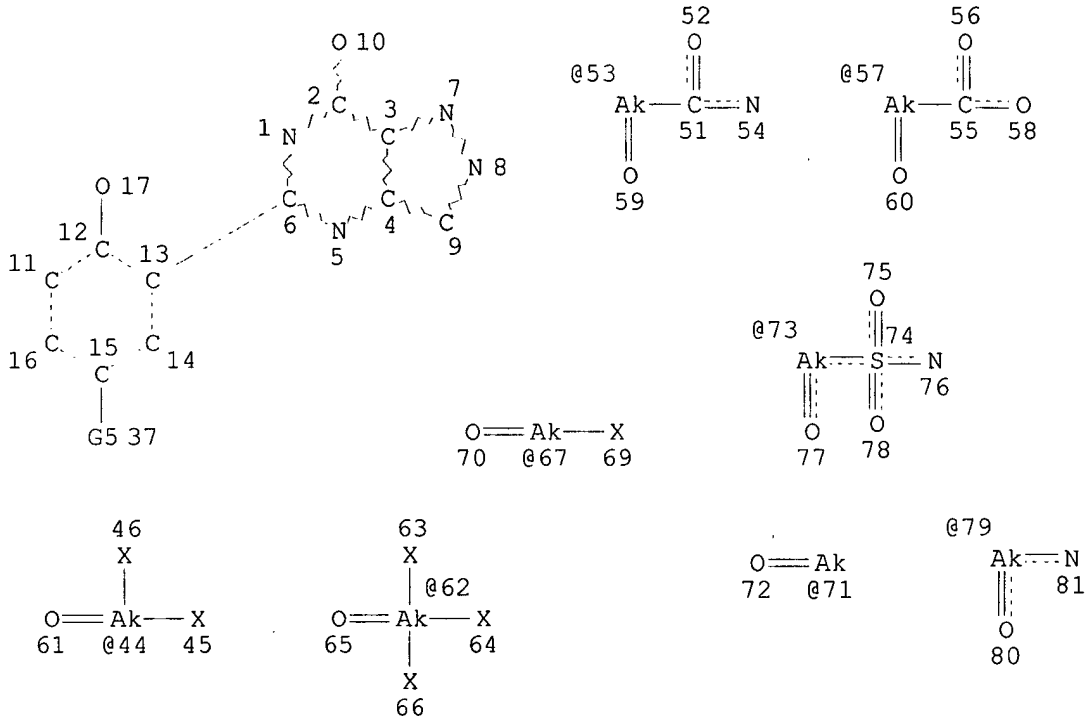

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L44 173 SEA FILE=REGISTRY ABB=ON PLU=ON L43 AND 1/NC
L45 152 SEA FILE=REGISTRY ABB=ON PLU=ON L44 NOT P/ELS
L46 140 SEA FILE=REGISTRY ABB=ON PLU=ON L45 AND NR<=4
L48 114 SEA FILE=REGISTRY ABB=ON PLU=ON L46 NOT (46.150.1 OR 46.156.30)/RID
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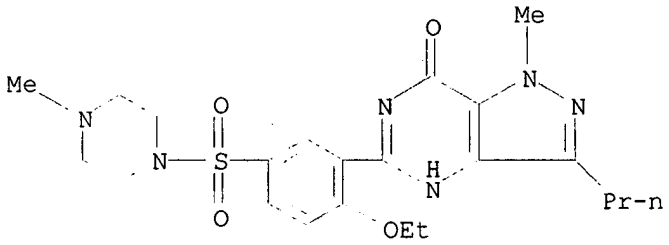

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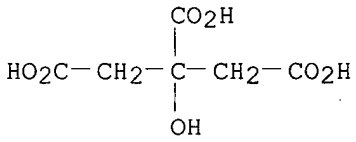

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REFERENCE 3: 138:70983

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REFERENCE 7: 138:66396

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REFERENCE 10: 138:44670

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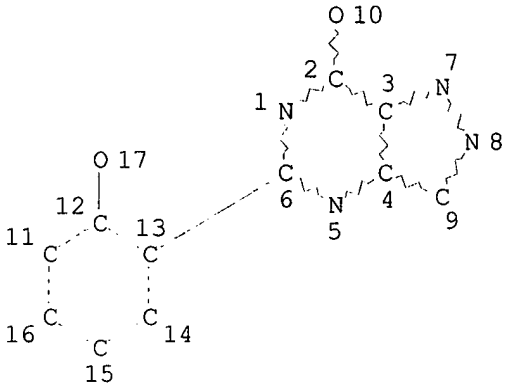

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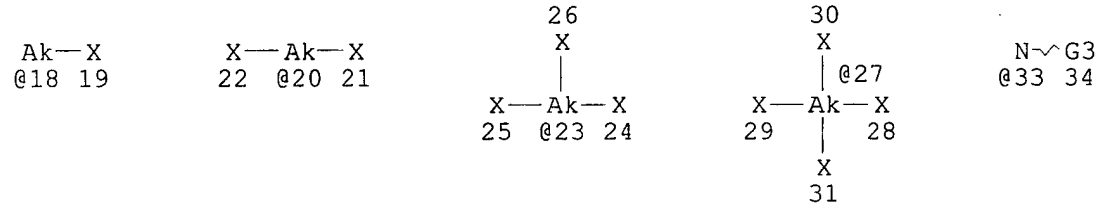

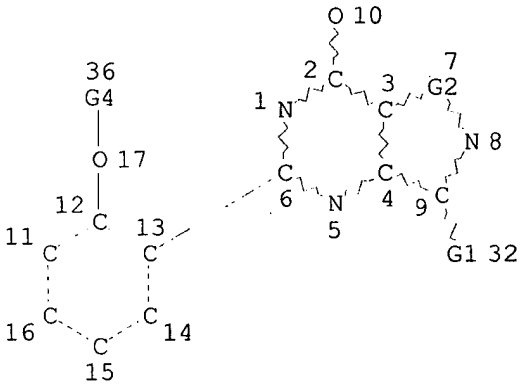

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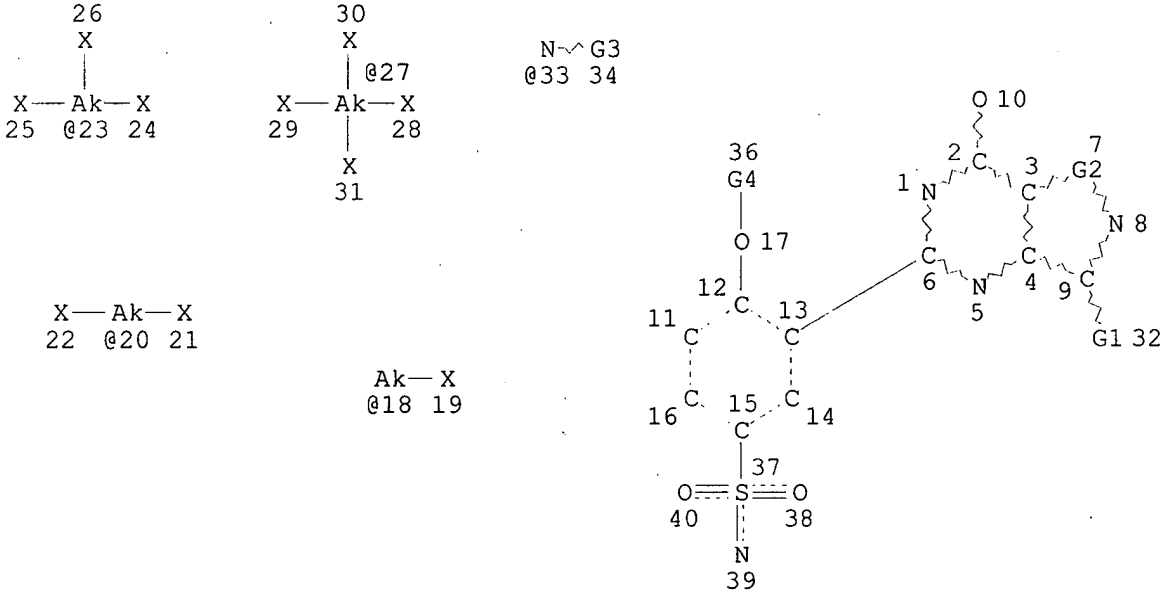

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 39

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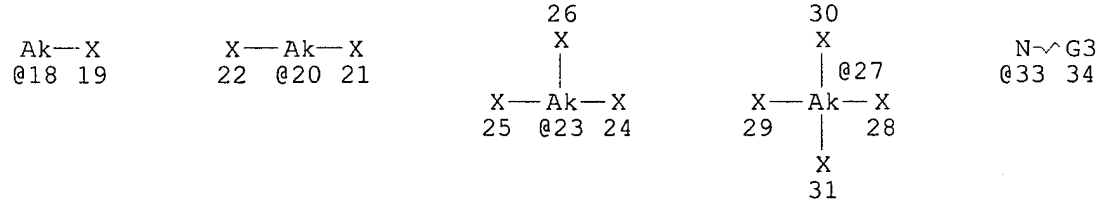
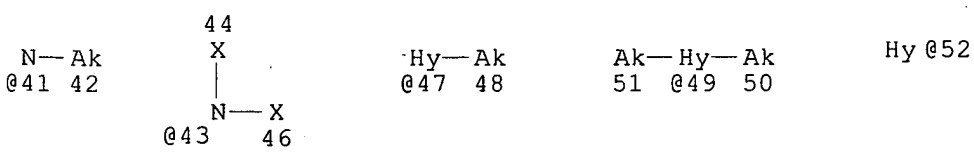




FILE COVERS 1907 - 26 Feb 2003 VOL 138 ISS 9
FILE LAST UPDATED: 25 Feb 2003 (20030225/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l79-l81
L84 10 (L79 OR L80 OR L81)

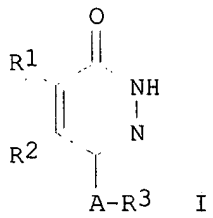
=> d all hitstr tot

L84 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:755213 HCAPLUS
DN 137:279206
TI Preparation of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications
IN Mylari, Banavara L.
PA USA
SO U.S. Pat. Appl. Publ., 39 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-506
ICS A61K031-501; C07D043-02; C07D413-02; C07D417-02
NCL 514249000
CC 28-15 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002143017	A1	20021003	US 2002-104664	20020321
	WO 2002079198	A1	20021010	WO 2002-IB320	20020131

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-280051P P 20010330
OS MARPAT 137:279206
GI



I

AB The present invention relates to novel pyridazinone compds. (shown as I; variables partially described below; e.g. 6-(2-indolylsulfonyl)-2H-pyridazin-3-one), pharmaceutical compns. comprising those compds. and to methods of using such compds. and compns. to inhibit aldose reductase, lower sorbitol levels and, thus, lower fructose levels, and/or treat or prevent diabetic complications such as diabetic **neuropathy**, diabetic retinopathy, diabetic nephropathy, diabetic cardiomyopathy, diabetic microangiopathy and diabetic macroangiopathy in mammals. This invention also relates to methods of affording cardioprotection to subjects not suffering from diabetes. This invention also relates to pharmaceutical compns. and kits comprising a combination of an aldose reductase inhibitor (ARI) of this invention and a sorbitol dehydrogenase inhibitor and to methods of using such compns. or kits to treat or prevent the above diabetic complications in mammals. This invention also relates to other combinations with the ARIs of this invention, including combinations with adenosine agonists; NHE-1 inhibitors; glycogen phosphorylase inhibitors; selective serotonin reuptake inhibitors; GABA agonists; antihypertensive agents; 3-hydroxy-3-methylglutaryl CoA reductase inhibitors; phosphodiesterase-5 inhibitors; and to glucose lowering agents. In I, A is S, SO or SO2; R1 and R2 are each independently H or Me; R3 is heteroaryl, -CHR4(heteroaryl) or NR6R7; R4 is H or (C1-C3)alkyl; R6 is (C1-C6)alkyl, aryl or heteroaryl; R7 is heteroaryl. No pharmacol. data is included. Although the methods of prepn. are not claimed, .apprx.50 example prepns. are included.

ST pyridazinone sulfenyl sulfinyl sulfonyl aldose reductase inhibitor diabetic complication; cardioprotective agent sulfenyl sulfinyl sulfonyl pyridazinone aldose reductase inhibitor

IT Angiotensin receptor antagonists
(angiotensin II; in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Cytoprotective agents
(cardioprotective; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors as)

IT Diabetes mellitus
(complications; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Heart, disease
(diabetic cardiomyopathy; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Blood vessel, disease
(diabetic macroangiopathy; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Blood vessel, disease
(diabetic microangiopathy; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Kidney, disease
(diabetic nephropathy; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT **Nerve, disease**
(diabetic **neuropathy**; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Eye, disease
(diabetic retinopathy; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Antiulcer agents

Ulcer
(foot; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Drug delivery systems
Test kits
(for sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Transport proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hydrogen ion-sodium-exchanging, inhibitors; in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Antihypertensives
GABA agonists
Purinoceptor agonists
(in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Heart, disease
(ischemia; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating)

IT Anti-ischemic agents
(prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating cardiac tissue ischemia)

IT Cataract
Human
(prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Drug delivery systems
(prodrugs; for sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT Antidiabetic agents
(thiazolidinedione derivs.; in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 60142-96-3, Gabapentin 134523-00-5, Atorvastatin **139755-83-2**, **Sildenafil** 148553-50-8, Pregabalin 399509-90-1, Vastatin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 9015-82-1 9028-21-1, Sorbitol dehydrogenase 9028-35-7, 3-Hydroxy-3-methylglutaryl CoA reductase 9035-74-9, Glycogen phosphorylase 9068-52-4, Phosphodiesterase-5
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 463976-07-0P, 6-(5-Chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-10-5P, 6-(5-Chloro-3-methylbenzofuran-2-sulfenyl)-2H-pyridazin-3-one
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 1131-07-3P, 5-Chloro-3-methylbenzofuran-2-carboxaldehyde 1430-25-7P, 3-Mercapto-6-methoxypyridazine 33118-83-1P, 5-Fluoro-3-methylbenzofuran 33118-84-2P, 5-Chloro-3-ethylbenzofuran 34848-65-2P, (2-Acetyl-4-fluorophenoxy)acetic acid 71643-66-8P, 4-Chloro-2-iodophenol 91063-19-3P, 3-Benzyloxy-6-chloropyridazine 248256-10-2P, 3-(4-Fluorophenyl)benzofuran 454181-75-0P, 3-Benzyloxy-6-

fluorosulfonylpyridazine 454182-03-7P, 3-Benzyloxy-6-mercaptopyridazine 463976-05-8P, 3-Methoxy-6-(indole-2-sulfenyl)pyridazine 463976-06-9P, 3-Methoxy-6-(indole-2-sulfonyl)pyridazine 463976-08-1P, 5-Chloro-2-mercapto-3-methylbenzofuran 463976-09-2P, 6-(5-Chloro-3-methylbenzofuran-2-sulfenyl)pyridazine 463976-11-6P, 3-Methoxy-6-(5-chloro-3-methylbenzofuran-2-sulfonyl)pyridazine 463976-19-4P, 3-Methoxy-6-(3-methylbenzofuran-2-sulfonyl)pyridazine 463976-21-8P, .alpha.,.alpha.,.alpha.-Trifluoro-o-iodo-p-cresol 463976-22-9P, 3-Methyl-5-trifluoromethylbenzofuran 463976-23-0P, 3-Methoxy-6-(5-trifluoromethyl-3-methylbenzofuran-2-sulfonyl)pyridazine 463976-25-2P, 3-Methoxy-6-[5-chloro-3-isopropylbenzofuran-2-sulfonyl]pyridazine 463976-28-5P, 3-Methoxy-6-(5-fluoro-3-methylbenzofuran-2-sulfonyl)pyridazine 463976-31-0P, 3-Methoxy-6-(3-hydroxybenzofuran-2-sulfonyl)pyridazine 463976-34-3P, 3-Methoxy-6-(5-chloro-3-methylbenzothiophene-2-sulfonyl)pyridazine 463976-40-1P, 3-Methoxy-6-(thieno[2,3-b]pyridine-2-sulfonyl)pyridazine 463976-43-4P, 4-Chloro-2-iodo-O-crotylphenol 463976-44-5P, 3-Methoxy-6-(5-chloro-3-ethylbenzofuran-2-sulfonyl)pyridazine 463976-46-7P, 6-[Imidazo[1,2-a]pyridine-3-sulfonyl]-3-methoxypyridazine 463976-47-8P, 3-Methoxy-6-(N-phenylsulfonylindole-2-sulfonyl)pyridazine 463976-60-5P, 3-Methoxy-6-(3-chloroindole-2-sulfenyl)pyridazine 463976-61-6P, 3-Methoxy-6-(3-chloroindole-2-sulfonyl)pyridazine 463976-63-8P, 3-Methoxy-6-(N-benzylindole-5-sulfonyl)-2H-pyridazine 463976-65-0P, 5-Chloro-3-methylbenzofuran-2-methanol 463976-66-1P, 2-Bromomethyl-5-chloro-3-methylbenzofuran 463976-67-2P, 3-Methoxy-6-(5-chloro-3-methylbenzofuran-2-methylsulfenyl)pyridazine 463976-68-3P, 3-Methoxy-6-(5-chloro-3-methylbenzofuran-2-methylsulfonyl)pyridazine 463976-70-7P, 3-Methoxy-6-(N-phenylsulfonylindole-3-sulfonyl)pyridazine 463976-71-8P, 3-Methoxy-6-(indole-3-sulfonyl)pyridazine 463976-73-0P, 6-(Indole-N-methyl-2-sulfonyl)-3-methoxypyridazine 463976-75-2P, 3-Methoxy-6-(pyrrole-1-sulfonyl)pyridazine 463976-82-1P, 3-Methoxy-6-(1,2,3,4-tetrahydroquinoline-1-sulfonyl)pyridazine 463976-90-1P, 3-Methoxy-6-(5-chloro-3-methylbenzofuran-2-sulfenyl)pyridazine 463976-91-2P, 3-Methoxy-6-(5-chloro-3-methylbenzofuran-2-sulfinyl)pyridazine
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 50-99-7, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(lowering agents; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors as)

IT 9028-31-3, Aldose reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 463976-04-7P, 6-(Indole-2-sulfonyl)-2H-pyridazin-3-one 463976-12-7P, 6-(Benzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-13-8P, 6-(5-Methoxybenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-14-9P, 6-(3,5-Dimethylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-15-0P, 6-(5,7-Dichlorobenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-16-1P, 6-(5-Chlorobenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-17-2P, 6-(4-Chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-20-7P, 6-(5-Trifluoromethyl-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-24-1P, 6-(5-Chloro-3-isopropylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-27-4P, 6-(5-Fluoro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-29-6P, 6-(6-Chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-30-9P, 6-(3-Hydroxybenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-32-1P, 6-(5-Chloro-3-hydroxybenzofuran-2-sulfonyl)-2H-pyridazin-3-

one 463976-33-2P, 6-(5-Chloro-3-methylbenzothiophene-2-sulfonyl)-2H-pyridazin-3-one 463976-35-4P, 6-(5-Methylbenzothiophene-2-sulfonyl)-2H-pyridazin-3-one 463976-36-5P, 6-(Benzothiophene-2-sulfonyl)-2H-pyridazin-3-one 463976-37-6P, 6-(3-Phenylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-38-7P, 6-[3-(4-Fluorophenyl)benzofuran-2-sulfonyl]-2H-pyridazin-3-one 463976-39-8P, 6-(Thieno[2,3-b]pyridine-2-sulfonyl)-2H-pyridazin-3-one 463976-41-2P, 2-(6-Oxo-1,6-dihydropyridazine-3-sulfonyl)-5H-furo[3,2-c]pyridin-4-one 463976-42-3P, 6-(5-Chloro-3-ethylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-45-6P, 6-(Imidazo[1,2-a]pyridine-3-sulfonyl)-2H-pyridazin-3-one 463976-48-9P, 6-(6-Chloroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-49-0P, 6-(5-Methoxyindole-2-sulfonyl)-2H-pyridazin-3-one 463976-50-3P, 6-(5-Chloroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-51-4P, 6-(6-Fluoroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-53-6P, 6-(5,6-Methylenedioxyindole-2-sulfonyl)-2H-pyridazin-3-one 463976-55-8P, 6-(5,7-Dichloroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-57-0P, 6-(7-Chloroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-58-1P, 6-(5-Chloro-3-phenylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one 463976-59-2P, 6-(3-Chloroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-62-7P, 6-(N-Benzylindole-5-sulfonyl)-2H-pyridazin-3-one 463976-64-9P, 6-(5-Chloro-3-methylbenzofuran-2-methylsulfonyl)-2H-pyridazin-3-one 463976-69-4P, 6-(Indole-3-sulfonyl)-2H-pyridazin-3-one 463976-72-9P, 6-(N-Methylindole-2-sulfonyl)-2H-pyridazin-3-one 463976-74-1P, 6-(Pyrrole-1-sulfonyl)-2H-pyridazin-3-one 463976-76-3P, 6-(Imidazole-1-sulfonyl)-2H-pyridazin-3-one 463976-77-4P, 6-(Indole-1-sulfonyl)-2H-pyridazin-3-one 463976-78-5P, 6-(3-Chloroindole-1-sulfonyl)-2H-pyridazin-3-one 463976-79-6P, 6-(3-Chloroindazole-1-sulfonyl)-2H-pyridazin-3-one 463976-80-9P, 6-(3-Methylindole-1-sulfonyl)-2H-pyridazin-3-one 463976-81-0P, 6-(1,2,3,4-Tetrahydroquinoline-1-sulfonyl)-2H-pyridazin-3-one 463976-83-2P, 6-(2,3-Dihydroindole-1-sulfonyl)-2H-pyridazin-3-one 463976-84-3P, 6-(5-Chloro-3-methylbenzofuran-2-sulfinyl)-2H-pyridazin-3-one 463976-85-4P, 6-(5-Chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one sodium salt 463976-86-5P, 6-(5-Fluoroindole-2-sulfonyl)-2H-pyridazin-3-one 463976-87-6P, 6-(Benzothiophene-3-sulfonyl)-2H-pyridazin-3-one 463976-88-7P, 6-(Furano[2,3-b]pyridine-2-sulfonyl)-2H-pyridazin-3-one 463976-89-8P, 6-(5-Methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 83-34-1, 3-Methylindole 95-15-8, Benzothiophene 100-51-6, Benzyl alcohol, reactions 106-48-9, 4-Chlorophenol 106-95-6, Allyl bromide, reactions 109-97-7, Pyrrole 120-72-9, Indole, reactions 141-30-0, 3,6-Dichloropyridazine 271-89-6, Benzofuran 272-01-5, Furano[2,3-b]pyridine 272-23-1, Thieno[2,3-b]pyridine 274-76-0, Imidazo[1,2-a]pyridine 288-32-4, Imidazole, reactions 352-13-6, 4-Fluorophenylmagnesium bromide 394-32-1 402-45-9, .alpha.,.alpha.,.alpha.-Trifluoro-p-cresol 496-15-1, 2,3-Dihydroindole 635-46-1, 1,2,3,4-Tetrahydroquinoline 1125-41-3, 5-Chloro-3-methylbenzofuran 1722-10-7, 3-Chloro-6-methoxypyridazine 3261-05-0, 5-Chloro-3-coumaranone 4784-77-4, Crotyl bromide 6921-66-0 7169-34-8, 3-Coumaranone 10075-51-1, N-Benzyl-5-bromoindole 10410-35-2, 3,5-Dimethylbenzofuran 13391-28-1, 5-Methoxybenzofuran 14315-14-1, 5-Methylbenzothiophene 16863-96-0, 3-Chloroindole 19404-18-3, 5-Chloro-3-methylbenzothiophene 23145-05-3, 5-Chlorobenzofuran 23145-06-4, 5,7-Dichlorobenzofuran 29110-74-5, 3-Chloroindazole 29909-72-6, 3-Phenylbenzofuran 31271-88-2, 6-Chloro-N-(p-tolylsulfonyl)indole 32617-55-3, 5-Chloro-N-(p-tolylsulfonyl)indole 38281-48-0, 2-Bromo-3-methylbenzofuran 40899-71-6, N-Phenylsulfonylindole 53497-58-8, 2-Mercaptoindole 54923-63-6, 5-Chloro-3-phenylbenzofuran 62226-17-9, 4-Chlorothieno[2,3-

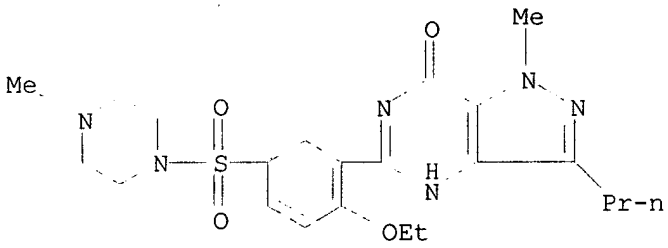
b]pyridine 80360-14-1, 3-Iodo-N-phenylsulfonylindole 139717-71-8, 5-Methoxy-N-(p-tolylsulfonyl)indole 143262-07-1, 7-Chloro-N-(p-tolylsulfonyl)indole 454182-00-4, 3-Fluorosulfonyl-6-methoxypyridazine 463976-18-3, 4-Chloro-3-methylbenzofuran 463976-26-3, 5-Chloro-3-isopropylbenzofuran 463976-52-5, 6-Fluoro-N-(p-tolylsulfonyl)indole 463976-54-7, 5,6-Methylenedioxy-N-(p-tolylsulfonyl)indole 463976-56-9, 5,7-Dichloro-N-(p-tolylsulfonyl)indole
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT 50-67-9, Serotonin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective reuptake inhibitors; in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

IT **139755-83-2, Sildenafil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with sulfenyl, sulfinyl and sulfonyl pyridazinone aldose reductase inhibitors for treating/preventing diabetic complications)

RN 139755-83-2 HCAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



L84 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:736115 HCAPLUS

DN 137:247711

TI Preparation of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors

IN Allerton, Charlotte Moira Norfor; Barber, Christopher Gordon; Kemp, Mark Ian

PA Pfizer Limited, UK; Pfizer Inc.

SO PCT Int. Appl., 96 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-505
ICS C07D487-04; A61P003-00; A61P015-00; A61P025-00; C07D487-04; C07D239-00; C07D231-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002074312	A1	20020926	WO 2002-IB679	20020307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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US 2001-291374P P 20010516
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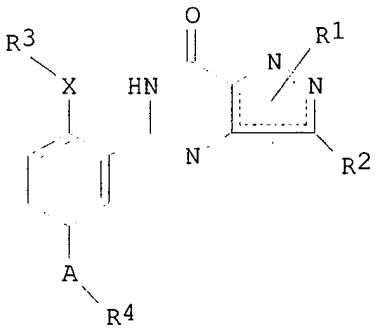


I

AB Pyrazolo[4,3-d]pyrimidinones (shown as I; e.g. 4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]butanoic acid (1)), or pharmaceutically or veterinarily acceptable salts, solvates, polymorphs or prodrugs thereof, which are useful in the curative and prophylactic treatment of a medical condition for which inhibition of a cyclic guanosine 3',5'-monophosphate phosphodiesterase (e.g. cGMP PDE5) is desired, are claimed. R1, R2, R3, R4, X and A have the meanings given herein. PDE5 and PDE6 inhibitory activities are reported for some of the claimed compds.; for example, 1 exhibits an IC50 of 1.8 nM for PDE5 and 163 nM for PDE6. Although the methods of prepn. are not claimed, 14 example prepns. of target compds. and 18 example prepns. of intermediates are included. In I, A represents C(O) or CH(OH); X represents O or NR5; R1, R3, R4 and R5 independently represent H, C1-C6 alkyl, Het, C1-C6 alkylHet, aryl, C1-C6 alkylaryl; or when X represents NR5 then R3 and R5 together with the N atom to which they are bound can form a heterocyclic ring. R2 represents H, halo, cyano, nitro, OR6, OC(O)R6, C(O)R6, C(O)OR6, NR6C(O)NR7R8, NR6C(O)OR6, OC(O)NR7R8, C(O)NR9R10, NR9R10, SO2NR9R10, SO2R11, C1-C6 alkyl, Het, C1-C6 alkylHet, aryl or C1-C6 alkylaryl. R6 represents H, C1-C6 alkyl, Het, C1-C6 alkylHet, aryl or C1-C6 alkylaryl. R7 and R8 independently represent H, C1-C6 alkyl, Het, C1-C6 alkylHet, aryl or C1-C6 alkylaryl; or R7 and R8 together with the N atom to which they are bound can form a heterocyclic ring. R9 and R10 independently represent H, C(O)R6, SO2R11, C1-C6 alkyl, Het, C1-C6 alkylHet, aryl or C1-C6 alkylaryl; or R9 and R10 together with the N atom to which they are bound can form a heterocyclic ring. R11 represents a C1-C6 alkyl, Het, C1-C6 alkylHet, aryl or C1-C6 alkylaryl group. Addnl. specifications for the above variables are given in the first claim.

ST pyrazolopyrimidinone prepn selective phosphodiesterase inhibitor; pyrimidinone pyrazolo prepn selective phosphodiesterase inhibitor

IT Blood vessel, disease
(Kawasaki; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and

selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Intestine
(anus, fissure; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT **Nervous system**
(autonomic, **neuropathy**; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Kidney, disease
(diabetic nephropathy; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT **Nerve, disease**
(diabetic **neuropathy**; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Cardiovascular system
(disease; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Sexual behavior
(disorder; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Drug delivery systems
(for pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

IT Stomach, disease
(gastroparesis; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Dialysis
(hemodialysis, stabilization of blood pressure during; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for)

IT Vein
(hemorrhoid; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Vasoconstriction
(hypoxic; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Sexual behavior
(impotence; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Neoplasm
(metastasis; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase

inhibitors for curative or prophylactic treatment of various medical conditions)

IT Skin, disease
(necrosis; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT **Nerve, disease**
(**neuropathy**; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Diabetes mellitus
(non-insulin-dependent; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Esophagus
(nutcracker; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT **Nerve, disease**
(peripheral **neuropathy**; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT **Nerve, disease**
(peripheral, diabetic **neuropathy**; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Parturition
(premature; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Alopecia
Alzheimer's disease
Anti-Alzheimer's agents
Antidiabetic agents
Antitumor agents
Cardiovascular agents
Diabetes insipidus
Diabetes mellitus
Dysmenorrhea
Multiple sclerosis
Neoplasm
Nervous system agents
Preeclampsia
Psoriasis
Tocolytic agents
(prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Animal
Human
(prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for use in)

IT Drug delivery systems
(prodrugs; for pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase

inhibitors)

IT Breathing (animal)
(respiratory failure; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Multiple sclerosis
(therapeutic agents; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT Drugs
(veterinary; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

IT 50-99-7, Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(impaired tolerance; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT 14797-55-8, Nitrate, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induced tolerance and tolerance; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors for curative or prophylactic treatment of various medical conditions)

IT 460346-81-0P, Methyl 4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]butanoate 460346-82-1P, Methyl 4-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-1-yl]butanoate
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(intermediate; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

IT 201663-12-9P, 5-Acetyl-2-butoxybenzoic acid 215298-75-2P, 4-(2-Propoxybenzoylamino)-3-propyl-1H-pyrazole-5-carboxamide 215298-77-4P, 5-(2-n-Propoxyphenyl)-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 215299-25-5P, 2-Cyanomethyl-5-(2-n-propoxyphenyl)-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 460346-87-6P, Methyl 5-acetyl-2-butoxybenzoate 460346-88-7P, Methyl 5-acetyl-2-isobutoxybenzoate 460346-89-8P, 5-Acetyl-2-isobutoxybenzoic acid 460346-90-1P, 4-[(5-Acetyl-2-butoxybenzoyl)amino]-5-ethyl-1H-pyrazole-3-carboxamide 460346-91-2P, 4-[(5-Acetyl-2-isobutoxybenzoyl)amino]-5-ethyl-1H-pyrazole-3-carboxamide 460346-92-3P, tert-Butyl 3-[4-[(5-acetyl-2-butoxybenzoyl)amino]-3-(aminocarbonyl)-5-ethyl-1H-pyrazol-1-yl]-1-azetidinecarboxylate 460346-93-4P, tert-Butyl 3-[4-[(5-acetyl-2-isobutoxybenzoyl)amino]-3-(aminocarbonyl)-5-ethyl-1H-pyrazol-1-yl]-1-azetidinecarboxylate 460346-94-5P, tert-Butyl 3-[5-(5-acetyl-2-butoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-1-azetidinecarboxylate 460346-95-6P, tert-Butyl 3-[5-(5-acetyl-2-isobutoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-1-azetidinecarboxylate 460346-97-8P, 5-(5-Acetyl-2-butoxyphenyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one mono(trifluoroacetate) 460346-99-0P, 5-(5-Acetyl-2-isobutoxyphenyl)-2-(3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one mono(trifluoroacetate) 460347-00-6P, 4-[(5-Acetyl-2-propoxybenzoyl)amino]-5-ethyl-1H-pyrazole-3-carboxamide **460347-01-7P**, 5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one 460347-02-8P, 4-[(5-Acetyl-2-propoxybenzoyl)amino]-5-propyl-1-(pyridin-2-ylmethyl)-1H-pyrazole-3-

carboxamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

IT 460346-72-9P, 5-(5-Acetyl-2-isobutoxyphenyl)-2-(1-cyclobutyl-3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 460346-73-0P, 5-(5-Acetyl-2-butoxyphenyl)-2-(1-isopropyl-3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 460346-74-1P, 5-(5-Acetyl-2-isobutoxyphenyl)-2-(1-isopropyl-3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 460346-75-2P, 5-(5-Acetyl-2-butoxyphenyl)-2-(1-cyclobutyl-3-azetidinyl)-3-ethyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one 460346-76-3P, tert-Butyl [5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]acetate 460346-77-4P, tert-Butyl [5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]acetate 460346-78-5P, tert-Butyl 3-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]-2-methylpropanoate 460346-80-9P, Ethyl 2-[5-(5-acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]propanoate 460346-83-2P, 4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-1-yl]butanoic acid 460346-84-3P, 4-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-Pyrazolo[4,3-d]pyrimidin-2-yl]butanoic acid 460346-85-4P, 2-[5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl]-N,N-dimethylacetamide 460346-86-5P, 5-(5-Acetyl-2-propoxyphenyl)-3-propyl-2-(2-pyridinylmethyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

IT 513-38-2, 1-Iodo-2-methylpropane 535-11-5, Ethyl 2-bromopropanoate 542-69-8, n-Butyl iodide 1191-95-3, Cyclobutanone 2675-89-0, 2-Chloro-N,N-dimethylacetamide 4897-84-1, Methyl 4-bromobutanoate 5292-43-3, tert-Butyl bromoacetate 16475-90-4, Methyl 5-acetylsalicylate 54090-36-7 76424-56-1, 4-Amino-3-propyl-1H-pyrazole-5-carboxamide 136685-85-3, tert-Butyl 3-bromo-2-methylpropanoate 150479-70-2 215298-74-1, 4-Amino-3-ethyl-1H-pyrazole-5-carboxamide 247582-83-8 254454-54-1, tert-Butyl 3-iodo-1-azetidinecarboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

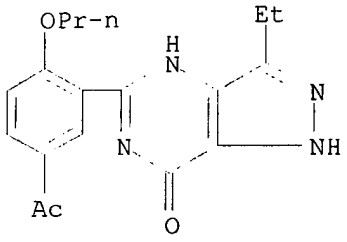
IT 9068-52-4, Cyclic guanosine 3',5'-monophosphate phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type 5; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Estrade, M; EUROPEAN JOURNAL OF PHARMACOLOGY 1998, V352(2/3), P157 HCAPLUS
(2) Pfizer Ltd; EP 0526004 A 1993 HCAPLUS
(3) Pfizer Ltd; WO 9428902 A 1994 HCAPLUS

IT **460347-01-7P**, 5-(5-Acetyl-2-propoxyphenyl)-3-ethyl-1,6-dihydropyrazolo[4,3-d]pyrimidin-7-one
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyrazolo[4,3-d]pyrimidinones as potent and selective type-5 cyclic guanosine 3',5'-monophosphate phosphodiesterase inhibitors)

RN 460347-01-7 HCAPLUS

CN 7H-Pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxyphenyl)-3-ethyl-1,4-dihydro- (9CI) (CA INDEX NAME)



L84 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:580166 HCAPLUS
TI Use of cGMP PDE5 inhibitors in the treatment of **neuropathy**: A review of the patent literature
AU Koppiker, Nandan
CS Pfizer Inc, Sandwich, CT13 9NJ, UK
SO IDrugs (2002), 5(5), 448-453
CODEN: IDRUFN; ISSN: 1369-7056
PB Current Drugs Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. In addn. to the classic roles that cyclic-3',5-guanosine monophosphate (cGMP) is thought to play in cell function regulation, such as smooth muscle regulation, inhibition of platelet aggregation, visual signal conduction, and neutrophil degranulation, it is now understood to be involved with various physiol. functions. The tissue levels and hence activity of cGMP are detd. by the balance between prodn. rates from guanosine triphosphate (GTP) through the guanylyl cyclase pathways, and degrdn. to GMP by specific cyclic nucleotide phosphodiesterases (PDEs). PDE5 inhibitors were initially developed for a possible role in cardiovascular disease; their role in the treatment of erectile dysfunction was brought to the forefront by the development of **sildenafil**. The focus of this article is the current patent literature around the use of PDE5 inhibitors for **neuropathy**. It also explores the possible hypotheses that may help to explain the mechanism(s) by which cGMP PDE5 inhibitors could have potential benefits in **neuropathy**.
ST review cGMP PDE5 inhibitor **neuropathy**
IT Human
(cGMP PDE5 inhibitors in treatment of **neuropathy**)
IT **Nerve, disease**
(**neuropathy**; cGMP PDE5 inhibitors in treatment of **neuropathy**)
IT 9068-52-4, phosphodiesterase 5
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; cGMP PDE5 inhibitors in treatment of **neuropathy**)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Allerton, C; WO 00127112 2001 HCAPLUS
(2) Asomoza-Espinosa, R; Eur J Pharmacol 2001, V418, P195 HCAPLUS
(3) Bhalay, G; WO 00177110 2001 HCAPLUS
(4) Bunnage, M; WO 09954333 1999 HCAPLUS
(5) Bunnage, M; WO 00024745 2000 HCAPLUS
(6) Bunnage, M; EP 00995751 2000 HCAPLUS
(7) Bunnage, M; WO 00127113 2001 HCAPLUS
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(24) Lincoln, T; Proc Natl Acad SCI USA 1976, V73, P2559 HCAPLUS
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(27) Maw, G; EP 01092719 2001 HCAPLUS
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(32) Soderling, S; J Biol Chem 1998, V273, P15553 HCAPLUS
(33) Sponsel, W; WO 00110406 2001 HCAPLUS
(34) Tanaka, T; WO 09500468 1995 HCAPLUS
(35) Thomas, M; J Biol Chem 1990, V265, P14964 HCAPLUS
(36) Thompson, W; Pharmacol Ther 1991, V51, P13 HCAPLUS
(37) Wood, A; EP 00995750 2000 HCAPLUS
(38) Wood, R; WO 00202118 2002 HCAPLUS
(39) Yamasaki, N; EP 00882718 1998 HCAPLUS

L84 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:72805 HCAPLUS
DN 136:139829
TI Compositions comprising sibutramine metabolites in combination with phosphodiesterase inhibitors
IN Jerussi, Thomas P.; Senanayake, Chrisantha H.; Fang, Qun K.
PA USA
SO U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Ser. No. 662,135.
CODEN: USXXCO
DT Patent
LA English
IC ICM A61K031-135
ICS A61K031-519
NCL 514340000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 17, 25
FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002010198	A1	20020124	US 2001-770663	20010129
	US 6476078	B2	20021105		
	US 6331571	B1	20011218	US 1999-372158	19990811
	US 6339106	B1	20020115	US 2000-662135	20000914
	WO 2002060424	A2	20020808	WO 2002-US2040	20020123

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-372158 A2 19990811
US 2000-662135 A2 20000914
US 1998-97665P P 19980824
US 1998-99306P P 19980902
US 2001-770663 A 20010129

AB Methods are disclosed for the treatment and prevention of disorders and conditions such as, but are not limited to: eating disorders; wt. gain; obesity; irritable bowel syndrome; obsessive-compulsive disorders; platelet adhesion; apnea; affective disorders such as attention deficit disorders, depression, and anxiety; male and female sexual function disorders; restless leg syndrome; osteoarthritis; substance abuse including nicotine and cocaine addiction; narcolepsy; pain such as **neuropathic** pain, diabetic **neuropathy**, and chronic pain; migraines; cerebral function disorders; chronic disorders such as premenstrual syndrome; and incontinence. Pharmaceutical compns. and dosage forms are also disclosed which comprise a racemic or optically pure sibutramine metabolite and an optional drug. Sibutramine free base was prepd. by the reaction of chlorbenzylnitrile dibromopropane in the presence of NaH in DMSO, followed by the treatment of the resulting 1-(4-chlorophenyl)cyclobutanecarbonitrile with isobutylmagnesium bromide and finally treatment with HCHO. The fee base was resolved into the (R) and (S) isomers and converted into their metabolites. Hard gelatin capsules contained racemic or optically pure sibutramine metabolite 5.0, microcryst. cellulose 90.0, pregelatinized starch 100.3, croscarmellose sodium 7.0, and Mg stearate 0.2 mg.

ST metabolite sibutramine phosphodiesterase inhibitor prepn

IT Epilepsy
(Lennox-Gastraut syndrome, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental disorder
(attention deficit disorder, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental disorder
(attention deficit hyperactivity disorder, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental disorder
(autism, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(capsules; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Alzheimer's disease
Analgesics
Anti-Alzheimer's agents
Antiarthritics
Anticonvulsants
Antidepressants
Antiobesity agents
Antiparkinsonian agents
Anxiolytics
Brain
Drug dependence
Parkinson's disease
Platelet aggregation inhibitors
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Muscarinic receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental activity
(consciousness, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT **Nerve, disease**
(diabetic **neuropathy**, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Memory, biological
Sexual behavior
(disorder, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Sexual behavior
(impotence, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Bladder
(incontinence, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Amnesia
Apnea
Coma
Schizophrenia
(inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(injections, s.c.; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Intestine, disease
(irritable bowel syndrome; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(mucosal; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Sleep
(narcolepsy, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental disorder
(obsession-compulsion; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(oral; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(parenterals; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Ovarian cycle
(premenstrual syndrome, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(rectal; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Leg
(restless leg syndrome; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Mental disorder
(senile psychosis, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Disease, animal
(speech disorder, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT Drug delivery systems
(tablets; compns. comprising sibutramine metabolites in combination

with phosphodiesterase inhibitor)
IT Drug delivery systems
(transdermal; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT Adrenoceptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.3; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(V and VI, inhibitors; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 50-67-9, 5-HT, biological studies 51-41-2, Norepinephrine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 153341-22-1P
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 106650-56-0P, Sibutramine 154752-44-0P 168835-59-4P 229639-54-7P 229639-55-8P 229639-56-9P 229639-57-0P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 109-64-8, 1,3-Dibromopropane 140-53-4, 4-Chlorobenzylnitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 28049-61-8P 84467-54-9P 84467-94-7P 84485-00-7P 106079-12-3P 153341-23-2P 259729-89-0P 259729-90-3P 259729-91-4P 259729-92-5P 259729-95-8P 259731-39-0P 259731-40-3P 389056-70-6P 389056-73-9P 389056-74-0P 391682-39-6P 391905-99-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 58-32-2, Dipyridamole 59-92-7, Levodopa, biological studies 76-42-6, Oxycodone 298-46-4, Carbamazepine 28860-95-9, Carbidopa 29925-17-5 37762-06-4, Zaprinast 42971-09-5, Vinpocetine 60142-96-3, Gabapentin 60719-84-8, Amrinone 61413-54-5, Rolipram 66104-22-1, Pergolide 68550-75-4, Cilostamide 74150-27-9, Pimobendan 74811-65-7, Croscarmellose sodium 77671-31-9, Enoximone 78415-72-2, Milrinone 81840-15-5, Vesnarinone **139755-83-2, Sildenafil** 391936-32-6, Peroximone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 50-36-2, Cocaine 54-11-5, Nicotine
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(dependence on; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT **139755-82-1**, Desmethylsildenafil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desmethylsildenafil; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)
IT 9004-34-6, Cellulose, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

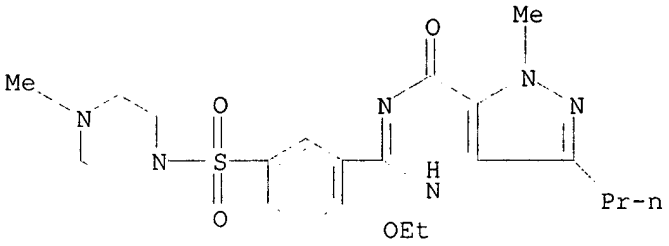
(microcryst.; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT 557-04-0 9005-25-8, Starch, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pregelatinized; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

IT **139755-83-2, Sildenafil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

RN 139755-83-2 HCAPLUS

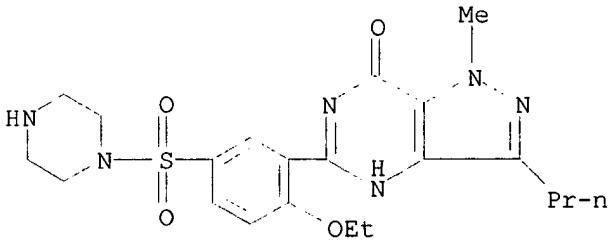
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



IT **139755-82-1,** Desmethylsildenafil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desmethylsildenafil; compns. comprising sibutramine metabolites in combination with phosphodiesterase inhibitor)

RN 139755-82-1 HCAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



L84 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:51989 HCAPLUS

DN 136:96083

TI Methods of using and compositions comprising (+)-sibutramine optionally in combination with other pharmacologically active compounds

IN Young, James W.; Jerussi, Thomas P.

PA USA

SO U.S. Pat. Appl. Publ., 14 pp., Cont.-in-part of U. S. Ser. No. 442,263.
CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-724
ICS A61K031-135

NCL 514648000

CC 1-11 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002006964	A1	20020117	US 2001-770393	20010129
	WO 2002060427	A2	20020808	WO 2002-US2038	20020123

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 1995-442263	A2	19950516
	US 2001-770393	A	20010129

AB This invention encompasses methods for the treatment and prevention of disorders that include, but are not limited to, eating disorders; wt. gain; obesity; irritable bowel syndrome; obsessive-compulsive disorders; platelet adhesion; apnea; affective disorders such as attention deficit disorders, depression, and anxiety; male and female sexual function disorders; restless leg syndrome; osteoarthritis; substance abuse including nicotine and cocaine addiction; narcolepsy; pain such as **neuropathic** pain, diabetic **neuropathy**, and chronic pain; migraines; cerebral function disorders; chronic disorders such as premenstrual syndrome; and incontinence. The invention further encompasses pharmaceutical compns. and dosage forms which comprise optically pure (+)-sibutramine, optionally in combination with a phosphodiesterase inhibitor or a lipase inhibitor.

ST sibutramine enantiomer resoln formulation combination therapy

IT Platelet (blood)
(adhesion; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Mental disorder
(affective; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Mental disorder
(attention deficit disorder; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Drug delivery systems
(capsules; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Appetite
Sexual behavior
(disorder; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Sexual behavior
(impotence; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Intestine, disease
(irritable bowel syndrome; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Drug delivery systems
(mucosal; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Mental disorder
(obsession-compulsion; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Drug delivery systems
(oral; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT Drug delivery systems
(parenteral; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT Adhesion, biological
(platelet; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT Drug delivery systems
(rectal; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT Drug delivery systems
(tablets; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT **Antidepressants**
Anxiolytics
Apnea
Obesity
Resolution (separation)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT Drug delivery systems
(transdermal; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT **139755-82-1**, Desmethylsildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desmethylsildenafil; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 9040-59-9, Cyclic nucleotide phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 84485-00-7P, Sibutramine hydrochloride 153341-23-2P, (-)-Sibutramine hydrochloride
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 154752-44-0P, (+)-Sibutramine
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 58-32-2, Dipyridamole 59-92-7, Levodopa, biological studies 76-42-6, Oxycodone 298-46-4, Carbamazepine 28860-95-9, Carbidopa 29925-17-5, Ro 20-1724 37762-06-4, Zaprinast 42971-09-5, Vinpocetine 60142-96-3, Gabapentin 60719-84-8, Amrinone 61413-54-5, Rolipram 66104-22-1, Pergolide 68550-75-4, Cilostamide 74150-27-9, Pimobendan 77671-31-9, Enoximone 78415-72-2, Milrinone 81840-15-5, Vesnarinone 84490-12-0, Piroximone **139755-83-2**, **Sildenafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 106650-56-0P, Sibutramine
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)
IT 109-64-8, 1,3-Dibromopropane 140-53-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(therapeutic compns. comprising (+)-sibutramine and optionally in

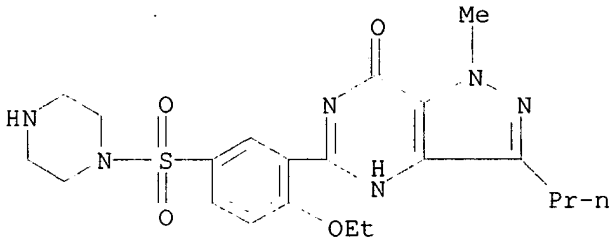
combination with other pharmacol. active compds.)

IT 28049-61-8P, 1-(4-Chlorophenyl)cyclobutanecarbonitrile 84467-54-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

IT **139755-82-1**, Desmethylsildenafil
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desmethylsildenafil; therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

RN 139755-82-1 HCAPLUS

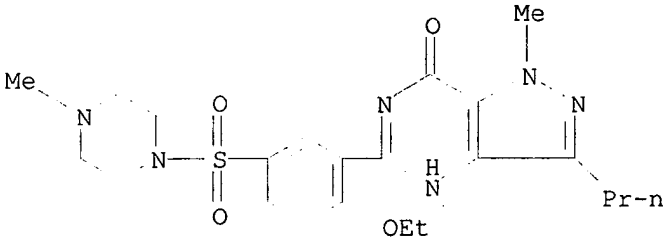
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



IT **139755-83-2, Sildenafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic compns. comprising (+)-sibutramine and optionally in combination with other pharmacol. active compds.)

RN 139755-83-2 HCAPLUS

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



L84 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:31259 HCAPLUS

DN 136:64173

TI Method using **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treating peripheral vascular diseases, peripheral **neuropathies**, and autonomic **neuropathies**

IN Wood, Ralph E.

PA USA

SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-495

CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002002118	A1	20020110	WO 2001-US41202	20010629
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2001079275	A5	20020114	AU 2001-79275	20010629
PRAI	US 2000-215065P	P	20000630		
	US 2000-219029P	P	20000718		
	WO 2001-US41202	W	20010629		

AB A method is provided for treating a patient suffering from peripheral vascular disease, peripheral **neuropathies**, or autonomic **neuropathies** by administering a cGMP PDE5 inhibitor such as **sildenafil**. The method is particularly applicable to patients suffering from diabetic foot ulcers, Raynaud's Phenomenon, CREST Syndrome, erythromatosis, rheumatoid diseases, diabetic retinopathies and onychomycosis. According to the invention, a cGMP PDE5 inhibitor may be administered as a prophylactic to patients predisposed to develop a peripheral vascular disease, peripheral **neuropathy**, or autonomic **neuropathy**.

ST vascular peripheral disease cGMP phosphodiesterase 5 inhibitor; peripheral autonomic **neuropathy** cGMP phosphodiesterase 5 inhibitor; **sildenafil** vascular peripheral disease peripheral autonomic **neuropathy**

IT Blood vessel, disease
(Raynaud's phenomenon; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT **Nervous system**
(autonomic, **neuropathy**; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Antiulcer agents
Diabetes mellitus
Foot
(diabetic foot ulcer; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Eye, disease
(diabetic retinopathy; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Disease, animal
(erythromatosis; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Nail (anatomical)
(onychomycosis; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT **Nerve, disease**
(peripheral **neuropathy**; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Blood vessel, disease

(peripheral; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Rheumatic diseases
(rheumatoid disease; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Connective tissue
(scleroderma, CREST syndrome variant; **sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT Drug delivery systems
Fungicides
(**sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

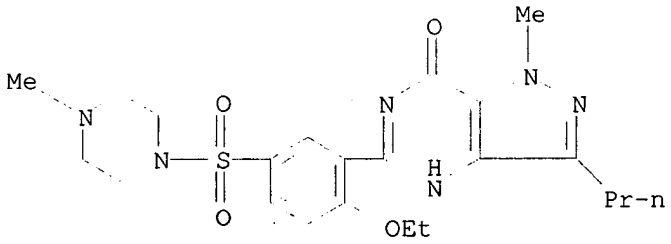
IT 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

IT **139755-83-2, Sildenafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bombrun; US 6043252 A 2000 HCAPLUS
(2) Graham; US 6075028 A 2000 HCAPLUS

IT **139755-83-2, Sildenafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sildenafil** or other cGMP phosphodiesterase 5 inhibitor for treatment of peripheral vascular diseases and peripheral and autonomic **neuropathies**)

RN 139755-83-2 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



L84 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:338762 HCAPLUS
DN 134:362292
TI Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
IN Farr, Spencer
PA Phase-1 Molecular Toxicology, USA
SO PCT Int. Appl., 222 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-68
ICS G01N033-50
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 1, 6, 7, 13, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001032928	A2	20010510	WO 2000-US30474	20001103
	WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

ST drug hypersensitivity gene expression DNA microarray app
IT Uncoupling protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1, 2 and 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(11 beta-hydroxysteroid dehydrogenase type II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(12-lipoxygenase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Metallothioneins
Presenilins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclin dependent kinase inhibitors
(1A; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Metallothioneins
Synaptobrevins
Thrombospondins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Connexins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(30; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Connexins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(32; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Syntaxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Connexins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(40; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Bone morphogenetic proteins
Keratins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(5-Aminolevulinate synthase 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(6-C-kine; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(60S ribosomal protein L6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Keratins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Apolipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A-I; methods of detg. individual hypersensitivity to a pharmaceutical

agent from gene expression profile)

IT Apolipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A-II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ACP (acyl-carrier); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ADP/ATP carrier; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ALDH1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ALDH2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ATF (activating transcription factor), ATF3 and ATF4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ATF-2 (activating transcription factor 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ATF4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ATP dep. helicase II (70kDa); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ATP dep. helicase II (Ku80); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(ATPase subunit 6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(B-myb; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Platelet-derived growth factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(BAG-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(BCRP; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(BRCA1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Sialoglycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(BSP II (bone sialoglycoprotein II); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bak; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bax (alpha); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bax; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bcl-xL; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Chemokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C-C, C10; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Chemokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(C-C, I-309; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Apolipoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C-III; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C-reactive; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C/EBP (CCAAT box/enhancer element-binding protein), .epsilon.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C/EBP-.alpha. (CCAAT box/enhancer element-binding protein .alpha.); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C4bp (complement C4b-binding protein); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C5a anaphylatoxin receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Complement receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C5a; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CAP (adenylate cyclase-assocd. protein); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT CD antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CD82; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CHD2 and CIG49; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CIDEB; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CLP; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CTCF; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Chemokine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CXCR4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CYP1A1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CYP4A; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Chk1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Clusterin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Csa-19; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D1, A1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DCC (deleted in colorectal cancer); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DEAD-box protein p72; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(DNA binding protein inhibitor ID-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA dependent helicase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA dependent protein kinase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Enzymes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA helicase II, ERCC3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Enzymes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA helicase II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Enzymes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA helicases; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA ligase IV; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA polymerase alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA repair protein XRCC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA topoisomerase I; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA-binding, APRF; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA-binding, p48; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(DNA-binding, zinc finger-contg., ZNF134; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DNA-binding, zinc finger-contg.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DOC-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(DRA; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Dopamine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D2(short); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Calbindins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D28k; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Calbindins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(D9k; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
Selectins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E-cadherin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E2F1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Apolipoproteins
Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(E; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ELAV-like neuronal protein-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ERA-B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ERCC-5; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ERCC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ERCC3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ERp72; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Egr-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FEN-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FIC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(FYN proto-oncogene; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Fra-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G/T mismatch binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G1, cyclin G1 interacting protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G6PD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(G; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GAS-7, GCLR, and GCLS; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GOS24; methods of detg. individuàl hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP (glucose-regulated protein), glucose-regulated protein 170; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP (glucose-regulated protein), glucose-regulated protein 58; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP78 (glucose-regulated protein, 78,000-mol-wt.); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP94; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GT mismatch binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gadd153; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Gadd45; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Garg-16; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ferritins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(H chain; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(H-CAM (homing cell adhesion mol.); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(H-cadherins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Histones
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(H2A; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Histones
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(H2B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HDLC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HIF-1 (hypoxia-inducible factor 1), .alpha.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HMG CoA reductase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT High-mobility group proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HMG1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HNF-4 (hepatocyte nuclear factor 4); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HNF4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heat-shock proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(HSP 27; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heat-shock proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HSP 47; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heat-shock proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HSP 70; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heat-shock proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HSP 90; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heat-shock proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HSP12; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(HSP70; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Hsp90; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I, II and III subunits for cytochrome oxidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Synaptotagmin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ICAM-1 (intercellular adhesion mol. 1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ICAM-2 (intercellular adhesion mol. 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ICAM-3 (intercellular adhesion mol. 3); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(ICE RelII; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ID-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Metallothioneins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IG; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Insulin-like growth factor-binding proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IGF-BP-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Insulin-like growth factor-binding proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IGF-BP-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Insulin-like growth factor-binding proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IGF-BP-3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Insulin-like growth factor-binding proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IGF-BP-5; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Synaptophysin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IL1B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IRF-7; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ISG-15; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ISGF-3 (interferon-stimulated gene factor 3); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Id2 (inhibitor of differentiation 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Immunoglobulin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IgG type I; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IkB-a; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Il-13; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Il-8; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I.kappa.B-.alpha. (inhibitor of RNA formation factor NF-.kappa.B, .alpha.); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JNK1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Jagged 1 and Jagged 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JunD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(K-cadherin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Keratins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(K17; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Ki67; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Animal cell
(Kupffer, bile duct epithelial cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L-FABP (liver fatty acid-binding protein); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L09604; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L13; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L13A, L37a, and S9; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L34; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(L6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Lipoprotein receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(LDL, low d. Lipoprotein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Liposin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MAD related protein 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MAP kinase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MBP (major basic protein); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MCL-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal

Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MEF-2 (myocyte-specific enhancer element-binding factor 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), MHC class II transactivator; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class I; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MLH1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MRTF1 (metal regulatory 1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MSH2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MSH2M; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MSH3 gene; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MSH3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Mcl-1 (myeloid cell leukemia sequence-1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Mim; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MnSOD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Mr 110,000; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(N-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(N-CAM; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NADH oxidoreductase subunit MWFE; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-A2 (nuclear factor A2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-E2 (nuclear factor erythroid 2), NF-E2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-III (nuclear factor III); methods of detg. individual

hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-IV (nuclear factor IV); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-.kappa.B (nuclear factor .kappa.B); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NMB; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NY-LU-12; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Steroid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Ner-1S; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Notch (receptor)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Notch1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Nucleosome assembly protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(OB-cadherin 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(OTK27; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(OX40 ligand; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(P-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(P170; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(P311; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PABP (poly(A)-binding protein); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PAPS synthetase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PARP; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PBX2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PCDH7; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PCNA; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PDGF assocd. protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PECAM-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PEG3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PIC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(PMS2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PTEN/MMAC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **Nerve**
(Purkinje cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD 51; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD23; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD50; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD51 homolog; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD52; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAG-1 (recombination-activating gene, 1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RANTES; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAP1A; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Retinoic acid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAR-.beta.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Retinoic acid receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RAR-.gamma.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT DNA formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RF-A (replication factor A); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT DNA formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RF-C (replication factor C); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribonucleoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RNA U1-contg., C; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Enzymes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RNA-unwinding, helicases; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RPS21, RPS24, RPS4X and S7; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.alpha.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.beta.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Retinoid X receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(RXR.gamma.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rad50; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rb, p107; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rb; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal

Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Ref-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Rel-B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Retinoid X receptor alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(S12; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(S21, S7 and RPS24; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(S4, X-linked; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribosomal proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(S4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SAA1 (serum amyloid A1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SAA2 (serum amyloid A2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SAA3 (serum amyloid A3); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glycophosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SCP2 (hydroxy steroid-carrier protein 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Sialoglycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SGP-2 (sulfoglycoprotein 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SII; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SMT3A and SMT3B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SOCS-1 (suppressor of cytokine signaling-1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SOCS-3 (suppressor of cytokine signaling-3); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SQM1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SRE-BP (steroid-responsive element-binding protein), 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SRF (serum response factor); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(STAT1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(STAT2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(STAT3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Sec23B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(Sod; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SoxS; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(T cell activation gene 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(T-cell cyclphilin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TCF-1 (T-cell factor 1); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TFIID (transcription factor IID); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TP53; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TRADD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TRAF2 (tumor necrosis factor receptor-assocd. factor 2); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(UCP2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(UDP-glucuronosyltransferase 2B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Annexins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(V; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(VAChT (vesicular acetylcholine transporter); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell adhesion molecules
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(VCAM-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(VCAM1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(VMAT; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Wnt-13; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(XP-C; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(XRCC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ZO-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(acute-phase, Major acute phase protein alpha-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(acyl CoA dehydrogenase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(adenine nucleotide translocator 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alc. dehydrogenase 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(alc. dehydrogenase 4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha-1 acid glycoprotein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha-2 macroglobulin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha-catenin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha-tubulin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macrophage inflammatory protein 2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macrophage
(alveolar; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(amyloid homolog; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(annexin V; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antiquitin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(apolipoprotein AII; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(apolipoprotein CIII; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell cycle
(arrest, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Heart, disease
(arrhythmia; methods of detg. individual hypersensitivity to a

pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(aspartate aminotransferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ataxia telangeictasia; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Phagocytosis
(autophagocytosis, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Natural products, pharmaceutical
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(belladonna; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(beta actin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Potassium channel
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(beta subunit; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bile acid-sodium-cotransporting; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bile acid-transporting, bile salt export pump; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bilirubin UDP-glucuronosyltransferase isoenzyme 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(biliverdin reductase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Spreading
(biol., genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macromolecular compounds
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(biol., prevention or repair of toxic damage of; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Neurotrophic factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(brain-derived; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(branched chain acyl-CoA oxidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-Ha-ras; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-abl; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-erbB2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-fms; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-fos; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-jun; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-myb; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(c-myc binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-myc; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calbindin D; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calnexin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calprotectins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calreticulin-B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calreticulin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(carnitine palmitoyl CoA transferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(caspase 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(caspase 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(caspase 7; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(caspase 8; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(catalase; methods of detg. individual hypersensitivity to a

pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(catechol-O-Me transferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cathepsin L; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(caveolins, Caveolin-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cdk4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Connective tissue
(cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Heart
Lung
(cells of; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Toxicity
(cellular, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ceruloplasmin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Biliary tract
(cholestasis; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Rhythm, biological
(circadian, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(clone 22 mRNA, alpha-1 splice variant; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(clone RP-11-468G5; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Collagens, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(collagen-alginate; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(collagenase type I interstitial; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Intestine
(colon; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(colony stimulating factor 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Estrogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conjugated; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(connexin 32; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(connexin 40; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(creatine kinase B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclin D3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclin G; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclin dependent kinase inhibitor p27kip1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cytochrome c oxidase subunit IV; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Mitochondria
(damage, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT DNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(damage, prevention; methods of detg. individual hypersensitivity to a

pharmaceutical agent from gene expression profile)
IT Cell differentiation
(de-differentiation, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Cytokine receptors
Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(death receptor 5; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(defender against cell death 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(defender against cell death-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(delta like; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Mental disorder
(dementia; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Hematopoiesis
(disorder, myelosuppression; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Elongation factors (protein formation)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(eEF-1.alpha., PTI-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Glycophosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(endoplasmins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Blood vessel
(endothelium; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(enolase alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Animal cell
(ependyma, meningothelial and leptomeningeal cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Lung
(epithelium, columnar ciliated; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(exchange factor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(excision repair ERCC3 and ERCC5 and ERCC6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Kidney, disease
(failure; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Carcinoembryonic antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(family member 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(farnesol receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fas antigen; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Liver, disease
(fatty; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ferritin H-chain; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Muscle
(fiber; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(flavin-contg. monooxygenase 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for .gamma.-interferon inducible early response gene F; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fosB; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gamma-glutamyl transpeptidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gap junction-specific; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene ERCC1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene L-myc; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene RAD52; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene cdc25; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT DNA formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene dnaC; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Vascular endothelial growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene flt 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene fyn; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene gadd153; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Lipoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(gene ospA; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene pim-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Agranulocytosis
Apoptosis
Cell adhesion
Cell aging
Cell migration
Mutation
Neoplasm
Recombination, genetic

Signal transduction, biological
Teratogenesis
Transformation, genetic
(genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Kidney, disease
(glomerulitis; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glucosylceramide synthase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutaredoxins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutathione S transferase theta-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutathione peroxidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutathione reductase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(glutathione synthetase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cell membrane
(glycoprotein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Intestine
(goblet cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth arrest specific protein 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth arrest specific protein 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth arrest-specific protein 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression

profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(growth arrest-specific protein 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hSNF2b; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hamartin, hamartin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(helicase like; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(heme-binding, 23; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hepatic lipase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Liver
(hepatocyte; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Immunophilins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(homolog ARA9; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Allergy
(hypersensitivity; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypoxanthine-guanine phosphoribosyltransferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypoxia inducible factor 1 alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Vaccines
(inactivated hepatitis; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitor of apoptosis protein 1; methods of detg. individual

hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitor of apoptosis protein 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Kidney, disease
(injury; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(insulin-like growth factor 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(insulin-like growth factor binding protein 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(integrin beta-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(intercellular adhesion mol.-3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interferon inducible protein 15; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interferon-inducible IP-10; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(involucrins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Natural products, pharmaceutical
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(ipecac; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(iron permease FTR1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Disease, animal

(irritation; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(junB; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(junD; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Animal cell
(juxtaglomerular, lacis and macula densa; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Immunoglobulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lambda heavy chain; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(leukemia inhibitory factor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Dyneins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(light chain 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lipopolysaccharide binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(lysyl oxidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Chemokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(macrophage inflammatory protein 1, alpha and beta; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macrophage migration inhibitory factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(macrophage inflammatory protein 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(macrophage-stimulating; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Lung
(macrophage; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mannose receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mdm-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(membrane; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Kidney
(mesangium; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Brain
(mesenchymal, capillary endothelial and fibroblasts cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metab.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metallothionein-IG; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Aging, animal
Allergy
Apparatus
Astrocyte
Bone
Brain
Bronchodilators
Computer program
DNA microarray technology
Digestive tract
Dione
Drugs
Eye
Fibroblast
Gallbladder
Hepatitis
Hyperplasia
Hypertension
Hypotension
Immunosuppression
Inflammation
Intestine
Jaundice
Kidney
Leukemia
Leukocyte
Liver
Macrophage
Mast cell
Muscle
Mutagenesis

Necrosis
Nucleic acid hybridization
Oligodendrocyte
Ovary
Pancreas
Plantago psyllium
Podophyllum (plant)
Sex
Skin
Spleen
Statistical analysis
Stomach
Testis
Thyroid gland
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
cDNA
mRNA
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Androgens
Polyoxyalkylenes, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT APC protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Androgen receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Aromatic hydrocarbon receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Biliproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT CD14 (antigen)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT CD44 (antigen)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT CFTR (cystic fibrosis transmembrane conductance regulator)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cadherins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Caldesmon
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Calnexin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Calreticulin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Carcinoembryonic antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Clusterin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclophilins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Dynamin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Eotaxin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Erythropoietin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Estrogen receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Fas antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Fas antigen

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Fas ligand
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Fibronectin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Filaggrin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Filamin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gelsolin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glucocorticoid receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gonadotropins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Hemopexins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Hepatocyte growth factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Hepatocyte growth factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Interleukin 10
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Interleukin 12
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent

from gene expression profile)
IT Interleukin 13
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 18
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 1.alpha.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 1.beta.
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Interleukin 8
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Lactoferrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Leukemia inhibitory factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Lymphotoxin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macrophage colony-stimulating factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Mannose receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Mdm2 protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Monocyte chemoattractant protein-1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Myelin basic protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Neurofibromin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Osteocalcins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Osteonectin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Osteopontin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Oxytocin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Potassium channel
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Prion proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Probes (nucleic acid)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Progesterone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proliferating cell nuclear antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Prostate-specific antigen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT RANTES (chemokine)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Stem cell factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT TCR (T cell receptors)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Tau factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Tenascins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Thioredoxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Thrombin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Thrombomodulin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transcortins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transferrin receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transferrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transforming growth factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transthyretin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Tropoelastins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Tumor necrosis factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Urokinase-type plasminogen activator receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Vimentins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Vitellogenins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT neu (receptor)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT p53 (protein)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **Neuroglia**

(microglia cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mig-2Or; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(monocyte chemotactic protein-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mss4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mta1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(myelin basic protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(myeloid cell differentiation protein-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(natural killer cell-enhancing factor B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(natural killer enhancing factor A; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(neomycin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Kidney, disease
(nephritis; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Toxicity
(nephrotoxicity; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Endocrine system
(neuroendocrine system, cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **Nerve**
(neuron; methods of detg. individual hypersensitivity to a

pharmaceutical agent from gene expression profile)
IT Toxins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(neurotoxins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Agranulocytosis
(neutropenia; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(non-specific cross reacting; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nucleic acid binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Animal cell
Blood
Blood serum
Urine
(nucleic acid or protein expression profile from; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nucleic acid-binding; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nucleoside diphosphate kinase beta isoform; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(octamer binding protein 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oncosis assocd.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(org. anion transporter 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(org. anion-transporting, MOAT-B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(org. anion-transporting; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ornithine decarboxylase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(osteopontin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oxygen regulated protein 150; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oxysterol binding protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p16INK4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p190-B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ras proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21c-Ha-ras; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21CIP1/WAF1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p27KIP1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Tumor necrosis factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p55; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p55CDC; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Tumor necrosis factor receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(p75; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Pancreas, disease
(pancreatitis, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pancreatitis-assocd. protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Insecticides
(pediculicides; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 109-A-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 117-B-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 134-A-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 134-A-4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 149-B-3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 239-A-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 240-A-4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 244-A-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(penicillin band 69-B-3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(penicillin band 77-C-2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **Nerve, disease**
(peripheral **neuropathy**; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteoglycans, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(perlecans; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisomal 3-oxoacyl-CoA thiolase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisomal acyl-CoA oxidase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisomal enoyl-CoA hydratase: 3-hydroxyacyl-CoA dehydrogenase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisome assembly factor 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisome assembly factor 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisome assembly factor-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisome biogenesis disorder protein 11; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(peroxisome biogenesis disorder protein 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(peroxisome biogenesis disorder protein 4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phenol sulfotransferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phenylalanine hydroxylase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phosphoenolpyruvate carboxykinase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phosphoglycerate kinase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phospholipase A2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Glycoproteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(plasma cell membrane; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(plasminogen activator inhibitor 2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(platelet/endothelial cell adhesion mol.-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Animal tissue
Organ, animal
Organelle
(prevention or repair of toxic damage of; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Nucleotides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prevention or repair of toxic damage of; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Collagens, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(procollagens, type I, alpha 1; methods of detg. individual

hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prohibitin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prohibitins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Peroxisome
(proliferation, genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(proline-rich; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prostaglandin H synthase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(protein tyrosine phosphatase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, general, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(proteinuria; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prothymosin, alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(psoriasin, 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Antibiotics
(quinolone, fluoroquinolones; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Intestine
(rectum; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Cytokines
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release' genes assocd. with; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(retinoic acid receptor gamma 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(retinol binding protein, CRBP-I (cellular retinol binding protein I); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(retinol binding protein, CRBP-II (cellular retinol binding protein II); methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Eye, disease
(retinopathy; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(senescence marker protein-30; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Animal cell
(serous, brush, and clara; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(silencer of death domain; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Vein
(sinusoidal, hepatic venule endothelial cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Ribonucleoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(small nuclear RNA-contg., B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Muscle
(smooth, cells; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Transport proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sodium taurocholate-cotransporting; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Hedgehog protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sonic; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(spermidine/spermine N1-acetyltransferase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Disease, animal
(steatosis; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Liver
(stellate cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stromelysin-1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(survivin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Phosphoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(synapsins, I; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Heart, disease
(tachycardia; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thiol-specific antioxidant protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thioredoxin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thymidine kinase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(thymidylate synthase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Heart
Kidney
Liver
Nerve
(toxicity; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transferrin receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transferrin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)
IT Gene, animal

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transthyretin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tryptophanyl-tRNA synthetase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ts11 gene encoding G1 progression protein; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Lung
(type I cell; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Activin receptors
Collagens, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ubiquitin conjugating enzyme; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Enzymes, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ubiquitin-conjugating, G2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Sterols
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(unsatd., Stanol, esters; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(urokinase plasminogen activator receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(vascular endothelial growth factor receptor 1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(very-long-chain acyl-CoA-dehydrogenase; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(vimentin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Epithelium
(visceral, parietal and tubular; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(visinin-like peptide; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(x13694; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(zinc finger protein 37; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Crystallins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.zeta.-crystallins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-2b; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Tubulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Thyroid hormone receptors
.alpha.1-Acid glycoprotein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Catenins
Integrins
Interferons
Peroxisome proliferator-activated receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.L; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Macroglobulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha.2-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Microglobulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(.alpha.2-microglobulins, .alpha.-2 microglobulin; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Chemokine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta. chemokine receptor CCR2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Chemokine receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta. chemokine receptor CCR5; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Actins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.-; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Interferons
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.2; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Integrins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.beta.4; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Fibrinogens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.gamma. chain; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Actins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.gamma.-actins; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT Interferons
Peroxisome proliferator-activated receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.gamma.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9038-14-6, Flavin containing monooxygenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1 and 3; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9059-22-7 9076-57-7, Histone deacetylase 52660-18-1 61969-98-0, Bilirubin-UDP-glucuronosyltransferase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9030-08-4, UDP-glucuronosyltransferase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(2 and 2B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 22916-47-8, Miconazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(2% cream; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9037-14-3, 5-Aminolevulinate synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(2, gene for; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 134678-17-4, Lamivudine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(3TC; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 99011-02-6, Imiquimod
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(5% cream; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-66-5
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(A and B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-60-9, Lactate dehydrogenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 8064-90-2, Trimeth/sulfa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Co-trimoxazole; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9015-85-4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I and III and IV; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-16-5, Cytochrome C oxidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(I, II and III, gene for; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-03-0
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(III; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 79871-54-8, Norgestimate-ethinyl estradiol mixt.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Norgestimate/ethinyl estradiol; methods of detg. individual

hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 50812-37-8, Glutathione S-transferase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Ya, theta-1, and alpha subunit; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9014-08-8, Enolase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alpha; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 58-82-2, Bradykinin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antagonist; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-15-4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(b; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 76901-00-3, Acetyl, hydrolase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(beta subunit; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 66722-44-9, Bisoprolol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bisoprolol/HCTZ; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9005-32-7, Alginic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(collagen-alginate; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 7440-57-5, Gold, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(compds.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9054-89-1, Superoxide dismutase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(copper-zinc-contg. and manganese-contg.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 154248-97-2, Imiglucerase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(injection; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 56-81-5, Glycerol, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(iodinated; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 50-02-2, Dexamethasone 50-06-6, Phenobarbital, biological studies 50-18-0, Cyclophosphamide 50-23-7, Hydrocortisone 50-24-8, Prednisolone 50-28-2, Estradiol, biological studies 50-44-2, 6-Thiopurine 50-48-6, Amitriptyline 50-55-5, Reserpine 50-76-0,

Actinomycin D 50-78-2, Aspirin 51-06-9, Procainamide 51-21-8, Fluorouracil 51-34-3, Scopolamine 51-48-9, Levothyroxine, biological studies 51-49-0, Dextrothyroxine 51-55-8, Atropine, biological studies 51-75-2, Mechlorethamine 52-01-7, Spironolactone 52-53-9, Verapamil 52-67-5, Penicillamine 52-86-8, Haloperidol 53-03-2, Prednisone 53-06-5, Cortisone 53-19-0, Mitotane 53-33-8, Paramethasone 53-86-1, Indomethacin 54-05-7, Chloroquine 54-11-5, Nicotine 54-31-9, Furosemide 54-36-4, Metyrapone 54-85-3, Isoniazid 55-63-0, Nitroglycerin 55-65-2, Guanethidine 55-98-1, Busulfan 56-54-2, Quinidine 56-75-7, Chloramphenicol 57-22-7, Vincristine 57-41-0, Phenytoin 57-53-4, Meprobamate 57-63-6, Ethinyl estradiol 57-66-9, Probenecid 57-83-0, Progestin, biological studies 57-96-5, Sulfinpyrazone 58-05-9, Leucovorin 58-14-0, Pyrimethamine 58-32-2, Dipyridamole 58-39-9, Perphenazine 58-54-8, Ethacrynic acid 58-55-9, Theophylline, biological studies 58-61-7, Adenosine, biological studies 58-74-2, Papaverine 58-93-5, Hydrochlorothiazide 58-94-6, Thiazide 59-05-2, Methotrexate 59-42-7, Phenylephrine 59-43-8, Thiamine, biological studies 59-92-7, Levodopa, biological studies 59-99-4, Neostigmine 60-40-2, Mecamylamine 60-54-8, Tetracycline 60-79-7, Ergonovine 60-87-7, Promethazine 61-32-5, Methicillin 61-72-3, Cloxacillin 64-75-5, Tetracycline hydrochloride 64-77-7, Tolbutamide 64-86-8, Colchicine 65-23-6, Pyridoxine 66-79-5, Oxacillin 66-97-7, Psoralen 67-20-9, Nitrofurantoin 67-45-8, Furazolidone 67-68-5, Dimethyl sulfoxide, biological studies 68-22-4D, Norethindrone, mixt. with ethinyl estradiol 68-41-7, Cycloserine 68-88-2, Hydroxyzine 69-53-4, Ampicillin 69-72-7, biological studies 69-89-6, Xanthine 73-24-5, 6-Aminopurine, biological studies 73-31-4, Melatonin 76-42-6, Oxycodone 76-57-3, Codeine 77-09-8, Phenolphthalein 77-19-0, Dicyclomine 77-36-1, Chlorthalidone 78-44-4, Carisoprodol 80-08-0, Dapsone 81-23-2, Dehydrocholic acid 81-81-2, Warfarin 82-92-8, Cyclizine 82-95-1, Buclizine 83-43-2, Methylprednisolone 83-73-8, Iodoquinol 83-89-6, Quinacrine 83-98-7, Orphenadrine 86-54-4, Hydralazine 89-57-6, Mesalamine 90-34-6, Primaquine 90-82-4, Pseudoephedrine 91-64-5, Coumarin 92-13-7, Pilocarpine 92-84-2, Phenothiazine 93-14-1, Guaifenesin 94-20-2, Chlorpropamide 94-36-0, Benzoyl peroxide, biological studies 94-78-0, Phenazopyridine 95-25-0, Chlorzoxazone 96-64-0, Soman 97-77-8, Disulfiram 99-66-1, Valproic acid 100-33-4, Pentamidine 100-97-0, Methenamine, biological studies 101-31-5, Hyoscyamine 103-90-2, Acetaminophen 113-18-8, Ethchlorvynol 113-42-8, Methylergonovine 113-45-1, Methylphenidate 114-07-8, Erythromycin 114-86-3, Phenformin 118-42-3, Hydroxychloroquine 122-09-8, Phentermine 123-56-8, Succinimide 123-63-7, Paraldehyde 124-94-7, Triamcinolone 125-29-1, Hydrocodone 125-33-7, Primidone 125-64-4, Methyprylon 125-71-3, Dextromethorphan 125-84-8, Aminoglutethimide 126-07-8, Griseofulvin 126-52-3, Ethinamate 127-07-1, Hydroxyurea 127-69-5, Sulfisoxazole 128-13-2, Ursodiol 130-95-0, Quinine 132-17-2, Benztropine 133-10-8, Sodium p-aminosalicylate 137-58-6, Lidocaine 138-56-7, Trimethobenzamide 144-11-6, Trihexyphenidyl 147-52-4, Nafcillin 147-94-4, AraC 148-82-3, Melphalan 154-21-2, Lincomycin 154-42-7, Thioguanine 154-93-8, Carmustine 155-97-5, Pyridostigmine 298-46-4, 5H-Dibenz[b,f]azepine-5-carboxamide 298-50-0, Propantheline 299-42-3, Ephedrine 300-62-9D, Amphetamine, mixed 300-62-9D, Amphetamine, mixed salts 302-17-0, Chloral hydrate 302-79-4, Tretinoin 303-53-7, Cyclobenzaprine 305-03-3, Chlorambucil 315-30-0, Allopurinol 321-64-2, Tacrine 346-18-9, Polythiazide 361-37-5, Methysergide 363-24-6, Dinoprostone 364-62-5, Metoclopramide 378-44-9, Betamethasone 389-08-2, Nalidixic acid 395-28-8, Isoxsuprine 439-14-5, Diazepam 443-48-1, Metronidazole 446-86-6, Azathioprine 456-59-7, Cyclandelate 461-72-3, Hydantoin 463-04-7, Amyl nitrite 469-62-5, Propoxyphene 474-25-9, Chenodiol 480-30-8, Dichloralphenazone 484-23-1, Dihydralazine 503-01-5, Isometheptene 512-15-2, Cyclopentolate 520-85-4, Medroxyprogesterone 525-66-6,

Propranolol 526-36-3, Xylometazoline 536-33-4, Ethionamide 541-15-1, Levocarnitine 546-88-3, Acetohydroxamic acid 555-30-6, Methyl dopa 564-25-0, Doxycycline 569-65-3, Meclizine 577-11-7, Docusate sodium 596-51-0, Glycopyrrolate 599-79-1, Sulfasalazine 603-50-9, Bisacodyl 634-03-7, Phendimetrazine 637-07-0, Clofibrate 657-24-9, Metformin 671-16-9, Procarbazine 672-87-7, Metyrosine 674-38-4, Bethanechol 723-46-6, Sulfamethoxazole 738-70-5, Trimethoprim 745-65-3, Alprostadil 791-35-5, Chlophedianol 797-63-7, Levonorgestrel 797-64-8D, L-Norgestrel, ethinyl estradiol mixt. 846-49-1, Lorazepam 846-50-4, Temazepam 911-45-5, Clomiphene 915-30-0, Diphenoxylate 962-58-3, Diazoxon 968-93-4, Testolactone 972-02-1, Diphenidol 990-73-8, Fentanyl citrate 1134-47-0, Baclofen 1143-38-0, Anthralin 1321-13-7, Potassium aminobenzoate 1397-89-3, Amphotericin B 1400-61-9, Nystatin 1404-04-2, Neomycin 1404-04-2D, Neomycin, mixt. with polymx/HC 1404-90-6, Vancomycin 1406-05-9, Penicillin 1491-59-4, Oxymetazoline 1622-61-3, Clonazepam 1953-02-2, Tiopronin 1977-10-2, Loxapine 2152-34-3, Pemoline 2152-44-5, Betamethasone valerate 2447-57-6, Sulfadoxine 2451-01-6, Terpin hydrate 2609-46-3, Amiloride 2809-21-4 2998-57-4, Estramustine 3116-76-5, Dicloxacillin 3313-26-6, Thiothixene 3385-03-3, Flunisolide 3485-14-1, Cyclacillin 3737-09-5, Disopyramide 3778-73-2, Iphosphamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 3930-20-9, Sotalol 4205-90-7, Clonidine 4419-39-0, Beclomethasone 4499-40-5, Oxtriphylline, biological studies 4618-18-2, Lactulose 4697-36-3, Carbenicillin 4759-48-2, Isotretinoin 5051-62-7, Guanabenz 5543-57-7, (s)-Warfarin 5633-20-5, Oxybutynin 5786-21-0, Clozapine 6190-39-2, Dihydroergotamine mesylate 6493-05-6, Pentoxifylline 6621-47-2, Perhexiline 7020-55-5, Clidinium 7235-40-7, Beta carotene 7261-97-4, Dantrolene 7416-34-4, Molindone 7439-93-2, Lithium, biological studies 7447-40-7, Potassium chloride, biological studies 7481-89-2, Zalcitabine 7487-88-9, Magnesium sulfate, biological studies 7648-98-8, Ambenonium 7681-11-0, Potassium iodide, biological studies 7681-93-8, Natamycin 7683-59-2, Isoproterenol 8029-99-0, Paregoric 8049-47-6, Pancreatin 8050-81-5, Simethicone 8063-07-8, Kanamycin 8067-24-1, Ergoloid mesylates 9001-27-8, BLood-coagulation factor VIII 9001-75-6, Pepsin 9004-10-8, Insulin, biological studies 9004-67-5, Methyl cellulose 9005-49-6, Enoxaparin, biological studies 9007-92-5, Glucagon, biological studies 9039-53-6, Urokinase 9046-56-4, Ancrod 10118-90-8, Minocycline 10238-21-8, Glyburide 10262-69-8, Maprotiline 10540-29-1, Tamoxifen 11041-12-6, Cholestyramine 11056-06-7, Bleomycin 11111-12-9, Cephalosporin 12174-11-7, Attapulgite 12244-57-4, Gold sodium thiomalate 12650-69-0, Mupirocin 12794-10-4D, Benzodiazepine, derivs. 13010-47-4, Lomustine 13292-46-1, Rifampin 13311-84-7, Flutamide 13392-28-4, Rimantadine 13647-35-3, Trilostane 14028-44-5, Amoxapine 14124-50-6 14611-51-9, Selegiline 14769-73-4, Levamisole 14838-15-4, Phenylpropanolamine 14882-18-9, Bismuth subsalicylate 15301-69-6, Flavoxate 15307-86-5, Diclofenac 15663-27-1, Cisplatin 15686-71-2, Cephalexin 15687-27-1, Ibuprofen 15722-48-2, Olsalazine 16051-77-7, Isosorbide mononitrate 16068-46-5, Potassium phosphate 16110-51-3, Cromolyn 16590-41-3, Naltrexone 16679-58-6, Desmopressin 17230-88-5, Danazol 17784-12-2, Sulfacytine 18323-44-9, Clindamycin 18559-94-9, Albuterol 18883-66-4, Streptozocin 19216-56-9, Prazosin 19794-93-5, Trazodone 20537-88-6, Amifostine 20830-75-5, Digoxin 20830-81-3, Daunomycin 21256-18-8, Oxaprozin 21829-25-4, Nifedipine 22204-53-1, Naproxen 22232-71-9, Mazindol 23031-32-5, Terbutaline sulfate 23214-92-8, Doxorubicin 23288-49-5, Probucol 25322-68-3, Polyethylene glycol 25451-15-4, Felbamate 25614-03-3, Bromocriptine 25812-30-0, Gemfibrozil 26652-09-5, Ritodrine 26787-78-0, Amoxicillin 26807-65-8, Indapamide 26839-75-8, Timolol **27203-92-5**, Tramadol 27262-47-1, Levobupivacaine 27686-84-6, Masoprocol

28395-03-1, Bumetanide 28657-80-9, Cinoxacin 28782-42-5, Difenoxin
28860-95-9, Carbidopa 28911-01-5, Triazolam 28981-97-7, Alprazolam
29094-61-9, Glipizide 29110-47-2, Guanfacine 29122-68-7, Atenolol
30516-87-1, Zidovudine 31441-78-8, Mercaptopurine 31677-93-7,
Bupropion hydrochloride 31828-71-4, Mexiletine 31883-05-3, Moricizine
32986-56-4, Tobramycin 33069-62-4, Paclitaxel 33419-42-0, Etoposide
34089-81-1, Sodium ferric gluconate 35189-28-7, Norgestimate
36322-90-4, Piroxicam 36505-84-7, Buspirone 36791-04-5, Ribavirin
38304-91-5, Minoxidil 40180-04-9, Tienilic acid 40580-59-4, Guanadrel
41575-94-4, Carboplatin 41708-72-9, Tocainide 42399-41-7, Diltiazem
42924-53-8, Nabumetone 49562-28-9, Fenofibrate 50679-08-8, Terfenadine
50925-79-6, Colestipol 50972-17-3, Bacampicillin 51022-71-0, Nabilone
51110-01-1, Somatostatin 51333-22-3, Budesonide 51384-51-1, Metoprolol
51481-61-9, Cimetidine 53179-11-6, Loperamide 53230-10-7, Mefloquine
53608-75-6, Pancrelipase 53714-56-0, Leuprolide 53994-73-3, Cefaclor
54024-22-5, Desogestrel 54063-53-5, Propafenone 54143-56-5, Flecainide
acetate 54182-58-0, Sucralfate 54350-48-0, Etretinate 54573-75-0,
Doxercalciferol 54910-89-3, Fluoxetine 55142-85-3, Ticlopidine
55268-75-2, Cefuroxime 55985-32-5, Nicardipine 56420-45-2, Epirubicin
58001-44-8 58581-89-8, Azelastine 59122-46-2, Misoprostol
59277-89-3, Acyclovir 59729-33-8, Citalopram 59865-13-3, Cyclosporine
A 60142-96-3, Gabapentin 60205-81-4, Ipratropium 61489-71-2,
Menotropin 61718-82-9, Fluvoxamine maleate 61869-08-7, Paroxetine
62571-86-2, Captopril 63585-09-1, Foscarnet sodium 63590-64-7,
Terazosin 64952-97-2, Latamoxef 65141-46-0, Nicorandil 65277-42-1,
Ketoconazole 66085-59-4, Nimodipine 66104-22-1, Pergolide
66357-35-5, Ranitidine 66376-36-1, Alendronate 67227-57-0, Fenoldopam
mesylate 68475-42-3, Anagrelide 68844-77-9, Astemizole 69049-73-6,
Nedocromil 69123-98-4, Fialuridine 69655-05-6, Didanosine
70359-46-5, Brominide tartrate 70989-04-7, S-Mephenytoin 71320-77-9,
Moclobemide 72432-03-2, Miglitol 72509-76-3, Felodipine 72956-09-3,
Carvedilol 73590-58-6, Omeprazole 74103-06-3, Ketorolac 74191-85-8,
Doxazosin 75330-75-5, Lovastatin 75695-93-1, Isradipine 75706-12-6,
Leflunomide 75847-73-3, Enalapril 76470-66-1, Loracarbef 76547-98-3,
Lisinopril 76568-02-0, Flosequinan 76584-70-8 76824-35-6, Famotidine
76932-56-4, Nafarelin 76963-41-2, Nizatidine 78110-38-0, Aztreonam
78628-80-5, Terbinafine hydrochloride 79516-68-0, Levocabastine
79617-96-2, Sertraline 79794-75-5, Loratadine 79902-63-9, Simvastatin
80125-14-0, Remoxipride 80474-14-2, Fluticasone propionate 81093-37-0,
Pravastatin 81098-60-4, Cisapride 81103-11-9, Clarithromycin
81669-57-0, Anistreplase 82410-32-0, Ganciclovir 82419-36-1, Ofloxacin
82626-48-0, Zolpidem 82834-16-0, Perindopril 83366-66-9, Nefazodone
83799-24-0, Fexofenadine 83881-51-0, Cetirizine 83905-01-5,
Azithromycin 84057-84-1, Lamotrigine 84449-90-1, Raloxifene
84625-61-6, Itraconazole 85441-61-8, Quinapril 85721-33-1,
Ciprofloxacin 86386-73-4, Fluconazole 86541-75-5, Benazepril
87333-19-5, Ramipril 87679-37-6, Trandolapril 88040-23-7, Cefepime
88150-42-9, Amlodipine 89365-50-4, Salmeterol 89778-26-7, Toremifene
90566-53-3, Fluticasone 91714-94-2, Bromfenac 92665-29-7, Cefprozil
93390-81-9, Fosphenytoin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 93413-69-5, Venlafaxine 93479-97-1, Glimepiride 93957-54-1,
Fluvastatin 95058-81-4, Gemcitabine 95233-18-4, Atovaquone
96036-03-2, Meropenem 97322-87-7, Troglitazone 97519-39-6, Ceftibuten
97534-21-9, Merbarone 97682-44-5, Irinotecan 98048-97-6, Fosinopril
98319-26-7, Finasteride 100986-85-4, Levofloxacin 102767-28-2,
Levetiracetam 103577-45-3, Lansoprazole 103628-46-2, Sumatriptan
104227-87-4, Famciclovir 104632-26-0, Pramipexole 105102-22-5,
Mometasone 105462-24-6 105857-23-6, Alteplase 106133-20-4,
Tamsulosin 106266-06-2, Risperidone 106392-12-5, Poloxamer 188

106650-56-0, Sibutramine 107753-78-6, Zafirlukast 107868-30-4, Exemestane 109889-09-0, Granisetron 111025-46-8, Pioglitazone 112809-51-5, Letrozole 112965-21-6, Calcipotriene 114798-26-4, Losartan 115103-54-3, Tiagabine 115956-13-3, Dolasetron mesylate 116644-53-2, Mibefradil 117976-89-3, Rabeprazole 119383-00-5 119914-60-2, Grepafloxacin 120014-06-4, Donepezil 121679-13-8, Naratriptan 122320-73-4, Rosiglitazone 122647-32-9, Ibutilide fumarate 122852-42-0, Alosetron 123948-87-8, Topotecan 124937-51-5, Tolterodine 126040-58-2, Calcium polycarbophil 127779-20-8, Saquinavir 129311-55-3, Ganirelix acetate 129318-43-0, Alendronate sodium 130209-82-4, Latanoprost 130929-57-6, Entacapone 134308-13-7, Tolcapone 134523-00-5, Atorvastatin 137862-53-4, Valsartan 138402-11-6, Irbesartan 143003-46-7, Alglucerase 144494-65-5, Tirofiban 144701-48-4, Telmisartan 145599-86-6, Cerivastatin 147059-72-1, Trovafloxacin 147245-92-9, Copolymer 1 150378-17-9, Indinavir 151096-09-2, Moxifloxacin 161814-49-9, Amprenavir 169590-42-5, Celecoxib **171599-83-0, Sildenafil citrate** 172820-23-4, Pexiganan acetate 180288-69-1, Trastuzumab 185243-69-0, Etanercept 188627-80-7, Eptifibatide 339524-26-4, Amiodorone 339524-30-0, Cyclopegic 339524-35-5, Cytoxin 339524-50-4, Hyperozia 339524-51-5, Navirapine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 107-97-1, Sarcosin 447-41-6, Nylidrin 8056-51-7 9000-86-6, Alanine aminotransferase 9000-97-9 9001-05-2, Catalase 9001-40-5, Glucose-6-phosphate dehydrogenase 9001-48-3, Glutathione reductase 9001-50-7, Glyceraldehyde 3-phosphate dehydrogenase 9001-62-1, Hepatic lipase 9001-84-7, Phospholipase A2 9002-03-3, Dihydrofolate reductase 9002-06-6, Thymidine kinase 9002-12-4, Urate oxidase 9002-67-9, Luteinizing hormone 9003-99-0, Myeloperoxidase 9012-25-3, Catechol-O-methyltransferase 9012-38-8, PAPS synthetase 9012-39-9 9012-52-6, S-Adenosylmethionine synthetase 9013-08-5, Phosphoenolpyruvate carboxykinase 9013-18-7, Fatty acyl-CoA synthetase 9013-38-1, Dopamine .beta.-hydroxylase 9013-66-5, Glutathione peroxidase 9013-79-0, Neuropathy target esterase 9014-55-5, Tyrosine aminotransferase 9015-71-8, Corticotropin releasing hormone 9015-81-0, 17-.beta. Hydroxysteroid dehydrogenase 9016-12-0, Hypoxanthine-guanine phosphoribosyltransferase 9023-44-3, Tryptophanyl-tRNA synthetase 9023-62-5, Glutathione synthetase 9023-64-7, .gamma.-Glutamylcysteinyl synthetase 9023-70-5, Glutamine synthetase 9024-60-6, Ornithine decarboxylase 9024-61-7, Histidine decarboxylase 9025-32-5, Prolidase 9026-00-0, Cholesterol esterase 9026-09-9, Phenol sulfotransferase 9026-43-1, Serine kinase 9026-51-1, Nucleoside diphosphate kinase 9027-13-8, Enoyl-CoA hydratase 9027-65-0, Acyl-CoA dehydrogenase 9028-06-2 9028-31-3, Aldose reductase 9028-35-7, HMG CoA reductase 9028-41-5, Hydroxyacyl-Coenzyme A dehydrogenase 9028-86-8, Aldehyde dehydrogenase 9029-73-6, Phenyl alanine hydroxylase 9029-80-5, Histamine N-methyltransferase 9029-97-4, 3-Ketoacyl-CoA thiolase 9031-37-2, Ceruloplasmin 9031-54-3, Sphingomyelinase 9031-61-2, Thymidylate synthase 9031-72-5, Alcohol dehydrogenase 9032-20-6, DT-Diaphorase 9035-58-9, Blood-coagulation factor III 9036-22-0, Tyrosine hydroxylase 9037-21-2, Tryptophan hydroxylase 9037-62-1, Glycyl tRNA synthetase 9039-06-9, NADPH cytochrome P450 reductase 9040-57-7, Ribonucleotide reductase 9041-92-3 9045-77-6, Fatty acid synthase 9046-27-9, .gamma.-Glutamyl transpeptidase 9048-63-9, Epoxide hydrolase 9055-67-8, Poly(ADP-ribose)polymerase 9059-25-0, Lysyl oxidase 9068-41-1, Carnitine palmitoyltransferase 9074-02-6, Malic enzyme 9074-10-6, Biliverdin reductase 9074-19-5, Hydratase 9074-87-7, .gamma.-Glutamyl hydrolase 9081-36-1, 25-Hydroxyvitamin D3 1-hydroxylase 11096-26-7, Erythropoietin 37205-63-3, ATP synthase 37237-44-8, Glucosylceramide synthase 37289-06-8, Acid ceramidase

37292-81-2, Cytochrome p 450 11A1 37318-49-3, Protein disulfide isomerase 39391-18-9, Prostaglandin H synthase 52228-01-0 56093-23-3, .alpha.-1,2-Fucosyl transferase 56645-49-9, Cathepsin G 59536-73-1, Phosphomannomutase 59536-74-2, Very long-chain acyl-CoA dehydrogenase 60267-61-0, Ubiquitin 60616-82-2, Cathepsin L 61116-22-1, Fatty acyl-CoA oxidase 62229-50-9, Epidermal growth factor 67339-09-7, Thiopurine methyltransferase 67763-96-6, Insulin-like growth factor 1 67763-97-7, Insulin-like growth factor II 77271-19-3, 6-O-Methylguanine-DNA methyltransferase 77847-96-2, Prostacyclin-stimulating factor 79747-53-8, Protein tyrosine phosphatase 79955-99-0, Stromelysin-1 80146-85-6, Tissue Transglutaminase 80295-41-6, Complement component C3 81627-83-0, Colony stimulating factor -1 82391-43-3, 12-Lipoxygenase 83268-44-4 83869-56-1, Granulocyte-macrophage colony-stimulating factor 85637-73-6, Atrial natriuretic factor 87397-91-9, Thymosin .beta.10 88943-21-9, Proteinase .alpha.1-inhibitor III 89964-14-7, Prothymosin, alpha 90698-26-3, Ribosomal protein S6 kinase 92767-51-6, O-6-Alkylguanine-DNA-alkyltransferase 96024-44-1, Granulin 105238-46-8, Macropain 106096-92-8, Fibroblast growth factor, acidic 106956-32-5, Oncostatin M 112130-98-0, Procathepsin L 114949-22-3, Activin (protein) 117698-12-1, Paraoxonase 119418-04-1, Galanin 123626-67-5, Endothelin-1 125978-95-2, Nitric oxide synthase 127464-60-2, Vascular endothelial growth factor 137632-07-6, Extracellular-signal-regulated kinase 1 138238-81-0, Endothelin converting enzyme-1 140208-24-8, Tissue inhibitor of metalloproteinase-1 141176-92-3 141349-86-2, Cyclin dependent kinase 2 141436-78-4, Protein kinase C 142243-03-6, Plasminogen activator inhibitor 2 142805-56-9, DNA topoisomerase II 142805-58-1, MAP kinase kinase 143180-75-0, DNA topoisomerase I 143375-65-9, Cyclin dependent kinase 1 145809-21-8, Tissue inhibitor of metalloproteinase-3 146480-35-5, Matrix metalloproteinase-2 147014-97-9, Cyclin dependent kinase 4 148348-15-6, Fibroblast growth factor 7 149316-81-4, Branched chain acyl-CoA oxidase 149371-05-1, Kinase (phosphorylating), gene c-abl protein 149885-78-9, Hepatocyte growth factor activator 154907-65-0, Checkpoint kinase 155807-64-0, FEN-1 Endonuclease 165245-96-5, p38 Mitogen-activated protein kinase 169592-56-7, CPP32 proteinase 179241-70-4, Protein kinase ZPK 179241-78-2, Caspase 8 182372-14-1, Caspase 2 182372-15-2, Caspase 6 182762-08-9, Caspase 4 187414-12-6, Caspase-1 189258-14-8, Caspase 7 192465-11-5, Caspase 5 193363-12-1, Vascular endothelial growth factor D 194554-71-7, Tissue factor pathway inhibitor 205944-50-9, Osteoprotegerin 220983-94-8, Sorbitol dehydrogenase 289898-51-7, JNK1 protein kinase 303752-61-6, DNA dependent protein kinase 329736-03-0, Cytochrome p450 3A4 329764-85-4, Cytochrome p450 1A1 329900-75-6, Cyclooxygenase 2 329978-01-0, Cytochrome p450 2C9 330196-64-0, Cytochrome p450 1A2 330196-93-5, Cytochrome p450 2E1 330207-10-8, Cytochrome p450 2B1 330589-90-7, Cytochrome p450 2C19 330596-22-0, Cytochrome p450 1B1 330597-62-1, Cytochrome p450 2D6 330975-22-9, Macrostatin 331462-97-6, Cytochrome p450 2B2 331462-98-7, Cytochrome p450 3A1 331823-00-8, Cytochrome p450 2C11 331823-12-2, Cytochrome p450 2C12 331823-27-9, Cytochrome p450 2A1 331827-06-6, Cytochrome p450 2A6 332847-52-6, Cytochrome p450 4A 336884-26-5, Cytochrome p450 2B10 338964-08-2, P 450 17A 338969-62-3, P 450 2A3 338969-69-0, P 450 2F2 338969-71-4, P 450 4A1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9004-02-8, Lipoprotein lipase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(precursor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 80449-02-1, Tyrosine protein kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(receptor; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9000-83-3, ATPase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(subunit 6; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9025-75-6
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(subunit B; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9079-67-8, NADH oxidoreductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(subunit MWFE, gene for; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9041-46-7
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type II; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9001-12-1, Collagenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type-1 interstitial; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

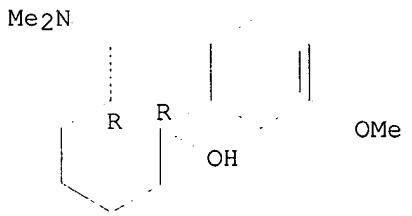
IT 60382-71-0, Diacylglycerol kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(zeta; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 9012-90-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(.alpha. and .beta.; methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **27203-92-5**, Tramadol **171599-83-0, Sildenafil citrate**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of detg. individual hypersensitivity to a pharmaceutical agent from gene expression profile)

RN 27203-92-5 HCAPLUS
CN Cyclohexanol, 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-, (1R,2R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

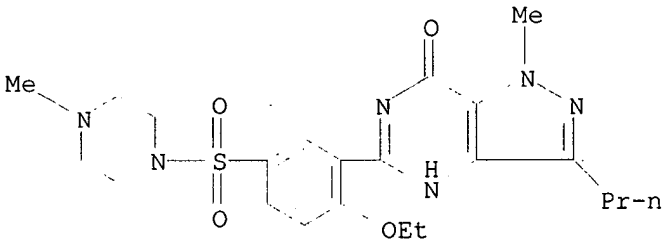


RN 171599-83-0 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-

d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

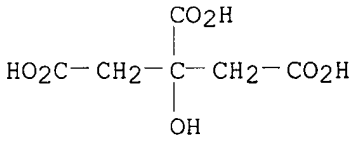
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

CRN 77-92-9
CMF C6 H8 O7



L84 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:283791 HCAPLUS
DN 134:290420
TI **Sildenafil** and other pyrazolopyrimidine derivatives for treatment of **neuropathies**
IN **Lareida, Jurg**
PA Switz.
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM A61K031-505
ICS A61P025-00
CC 1-11 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026659	A1	20010419	WO 2000-CH409	20000727
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	EP 1220672	A1	20020710	EP 2000-943518	20000727
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRAI CH 1999-1862 A 19991012
WO 2000-CH409 W 20000727
OS MARPAT 134:290420
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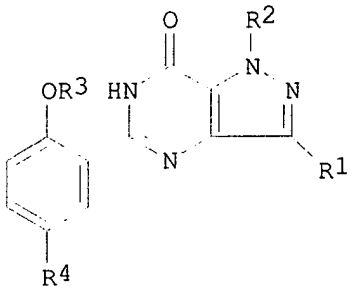


I

AB Compds. I (R1 = C1-6 alkyl, optionally halo-substituted; R2 = H, C1-4 alkyl, optionally halo-substituted or replaced by halo; R3 = C2-4 alkyl, optionally halo-substituted; R4 = SO2NR5R6, CO2R7 etc.; R5, R6 = H, C1-4 alkyl, or, together with the N atom to which they are attached, form pyrrolidino, piperidino, morpholino, etc.; R7 = H, C1-4 alkyl, optionally fluoro-substituted), or the pharmaceutically acceptable salts thereof, are useful for the chemotherapeutic treatment of **neuropathies**.

ST **sildenafil neuropathy** treatment; pyrazolopyrimidine deriv **neuropathy** treatment

IT **Nerve, disease**
(diabetic **neuropathy**; **sildenafil** and other pyrazolopyrimidine derivs. for **neuropathy** treatment)

IT **Nerve, disease**
(**neuropathy**; **sildenafil** and other pyrazolopyrimidine derivs. for **neuropathy** treatment)

IT **Nervous system agents**
(**sildenafil** and other pyrazolopyrimidine derivs. for **neuropathy** treatment)

IT **139755-83-2, Sildenafil**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sildenafil** and other pyrazolopyrimidine derivs. for **neuropathy** treatment)

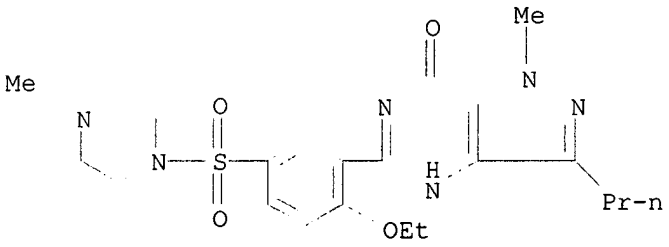
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Brewer, M; MOVEMENT DISORDERS 1998, V13(5), P860
(2) Graham, R; US 6075028 A 2000 HCAPLUS
(3) Hamilton, H; US 4666908 A 1987 HCAPLUS
(4) Nurnberg, H; JOURNAL OF CLINICAL PSYCHIATRY 1999, V60(1), P33 HCAPLUS
(5) Pfizer Ltd; WO 9307149 A 1993 HCAPLUS
(6) Rendell, M; JAMA, THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1999, V281(5), P421 HCAPLUS
(7) Scope, D; NEUROLOGY 2000, V54(7), Pa90
(8) Zesiewicz, T; NEOROLOGY 1999, V52(6), P215

IT **139755-83-2, Sildenafil**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sildenafil** and other pyrazolopyrimidine derivs. for **neuropathy** treatment)

RN 139755-83-2 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX

NAME)



L84 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:114953 HCAPLUS
DN 134:157562
TI Methods and pharmaceutical compositions for increasing optic nerve, choroidal and retinal blood flow by cyclic-GMP analogs, cyclic-GMP phosphodiesterase inhibitors, or guanylate cyclase activators.
IN Sponsel, William E.
PA Board of Regents, the University of Texas System, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K009-00
CC 1-8 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001010406	A2	20010215	WO 2000-US21929	20000810
	WO 2001010406	A3	20020808		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1246605	A2	20021009	EP 2000-952721	20000810
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003506394	T2	20030218	JP 2001-514927	20000810
PRAI	US 1999-148150P	P	19990810		
	WO 2000-US21929	W	20000810		

AB A method is provided for improving visual function and maximizing the health of the optic nerve and retina by increasing blood flow velocity therein through the application of an effective amt. of a formulation of an agent that is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator. Compds. of the invention include e.g. **sildenafil citrate** (**Viagra**).
ST optic nerve choroid retina circulation enhancer cGMP analog; guanylate cyclase activator ocular circulation enhancer; choroid retinal blood flow cGMP phosphodiesterase inhibitor; antiischemic pharmaceutical **sildenafil citrate** eye disease
IT Disease, animal
(atrophy, macular retinal pigment epithelial; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator

for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye
(choroid, ischemic disorder of; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(controlled-release, films; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Anti-ischemic agents
Cardiovascular agents
Vision
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Nitrosamines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Ischemia
(diabetic choroidal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(gels, ophthalmic; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Hypertension
(intracranial, benign; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Capillary vessel
(leakage syndrome, macular edema with; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(macula, degeneration, wet age related and non-age related; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Hypertension
(macular disorder related to; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(macular hole; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(neovascularization, choroidal and inflammatory subretinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(neovascularization, degenerative subretinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Angiogenesis
(neovascularization, eye, choroidal and inflammatory subretinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate

cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Angiogenesis
(neovascularization, eye, degenerative subretinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Angiogenesis
(neovascularization, retinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT **Nerve, disease**
(**neuropathy**, ischemic, toxic, traumatic, and idiopathic optic; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT **Nerve, disease**
(**neuropathy**, normotensive excavatory optic; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Vein
(occlusion, branch retinal; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Lipofuscins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ocular accumulation; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Blood vessel, disease
(ocular, angioma; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Circulation
(ocular, enhancers of; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Drug delivery systems
(ophthalmic, controlled-release, metered dose device; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Drug delivery systems
(ophthalmic, controlled-release, semisolid; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Drug delivery systems
(ophthalmic; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT **Nerve**
(optic, drusen; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Drug delivery systems
Drug delivery systems
(oral; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT Eye, disease
(papillitis; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal

and retinal blood flow.)
IT Drug delivery systems
(parenterals; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(retina, detachment, pigment epithelial; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye
(retina, idiopathic telangiectasis of; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(retina, neovascularization; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(retinitis pigmentosa; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(retinitis, neuro-; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(solns., ophthalmic; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(solns.; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(suspensions; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(toxic maculopathy; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Drug delivery systems
(transdermal, controlled-release; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT Eye, disease
(uveitis; cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT **139755-83-2, Sildenafil 171599-83-0, Sildenafil citrate**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)
IT 55-63-0, Nitroglycerin 58-32-2, Dipyridamole 302-01-2D, Hydrazine, derivs., biological studies 7632-00-0, Sodium nitrite 7665-99-8D, Cyclic-GMP, derivs. 7803-49-8, Hydroxylamine, biological studies 8001-81-8D, Carboline, derivs. 12766-00-6D, Quinazolinone, derivs. 13010-20-3D, Nitrosurea, derivs. 15078-28-1, Nitroprusside 26628-22-8, Sodium azide 37762-06-4, Zaprinast 57076-71-8, Denbufylline

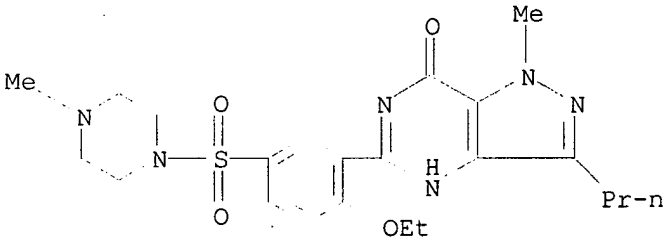
101975-10-4, Zardaverine 141184-34-1, Filaminast 144035-83-6, Piclamilast
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT 7665-99-8, Cyclic-GMP
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT 9054-75-5, Guanylate cyclase 9068-52-4, Cyclic-GMP phosphodiesterase 10102-43-9, Nitric oxide, biological studies 125978-95-2, Nitric oxide synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT **139755-83-2, Sildenafil 171599-83-0, Sildenafil citrate**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

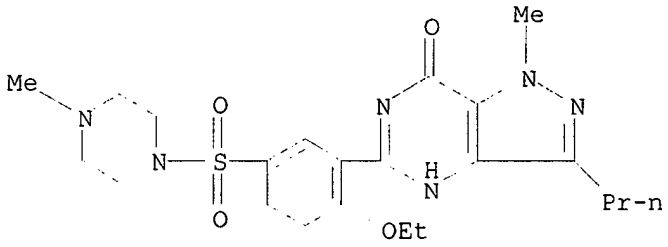
RN 139755-83-2 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



RN 171599-83-0 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

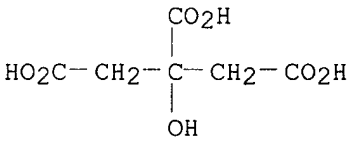
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

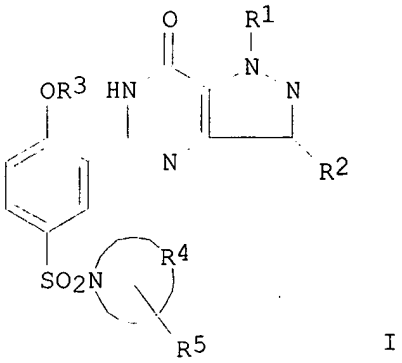
CRN 77-92-9
CMF C6 H8 O7



L84 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:98405 HCAPLUS
DN 134:141774
TI Methods, pharmaceutical compositions comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors for prophylactic and treatment of diseases and conditions of the eye
IN Laties, Alan Malev
PA Pfizer Products Inc., USA
SO Eur. Pat. Appl., 9 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM A61K031-519
ICS A61P027-02; A61P027-06
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1074258	A2	20010207	EP 2000-306235	20000721
	EP 1074258	A3	20010418		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001048788	A2	20010220	JP 2000-222162	20000724
	US 2002119974	A1	20020829	US 2002-126375	20020419
PRAI	US 1999-146095P	P	19990728		
	US 2000-607562	B1	20000629		

OS MARPAT 134:141774
GI



I

AB The invention describes methods using cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors (I) [R1= H, C1-C3 alkyl, C3-C5 cycloalkyl, perfluoroalkyl; R2= H, (hydroxyl-substituted) C1-C6 alkyl, C3-C6 cycloalkyl, etc.; R3= C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, etc.; R4N completes pyrrolidinyl, morpholino, etc.; R5= H, C1-C4 alkyl, C1-C3 alkoxy, etc.] for prophylactic and therapeutic administration in patients with eye diseases and conditions including:central retinal artery occlusion; central retinal vein occlusion; optic **neuropathy** including, but not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**; and macular (dry) degeneration. Pharmaceutical compns. comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors are also disclosed.

ST cyclic GMP phosphodiesterase inhibitor pharmaceutical eye disease

IT Glaucoma (disease)
(low-tension; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Eye, disease
(macula, degeneration, (dry); phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT **Nerve, disease**
(**neuropathy**, optic; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Vein
(occlusion, central retinal; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Artery, disease
(occlusion, eye posterior ciliary body; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

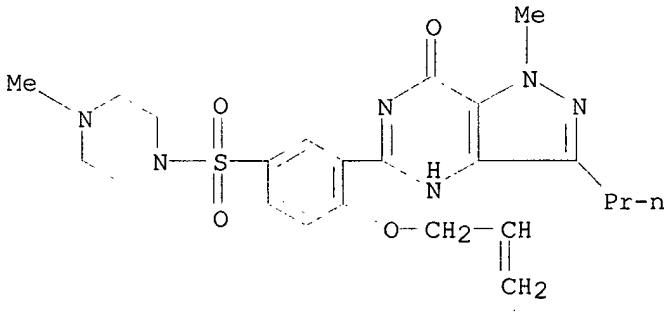
IT Heart, disease
(optic **neuropathy** assocd. with family history of; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Corticosteroids, biological studies
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(optic **neuropathy** assocd. with intake of; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

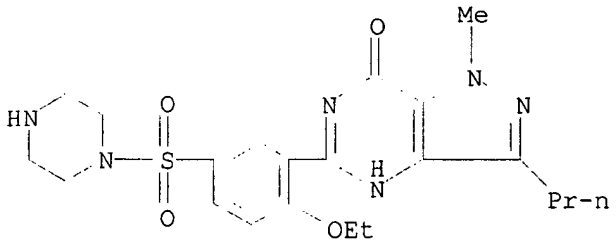
IT Surgery
(optic **neuropathy** assocd. with intraocular; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT Diabetes mellitus
Hypertension
Inflammation
(optic **neuropathy** assocd. with; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

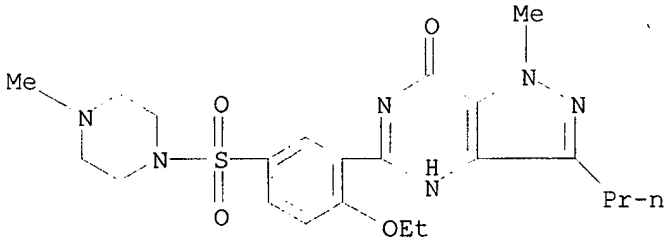
IT **Nerve**
(optic, **neuropathy**, anterior ischemic and glaucomatous; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT Antiglaucoma agents
Eye, disease
Glaucoma (disease)
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT Eye, disease
(retina, ischemia, central retinal artery occlusion; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT Blood pressure
(venous, glaucoma assocd. with episcleral; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT **139755-81-0 139755-82-1 139755-83-2 139755-84-3 139755-85-4 139755-86-5 139755-87-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT 9068-52-4, Cyclic guanosine 3',5'-monophosphate phosphodiesterase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(type 5; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
IT **139755-81-0 139755-82-1 139755-83-2 139755-84-3 139755-85-4 139755-86-5 139755-87-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)
RN 139755-81-0 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-(2-propenyloxy)phenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



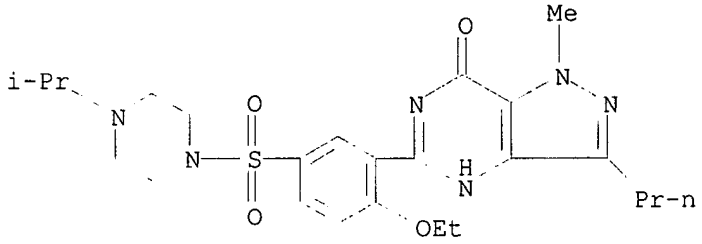
RN 139755-82-1 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



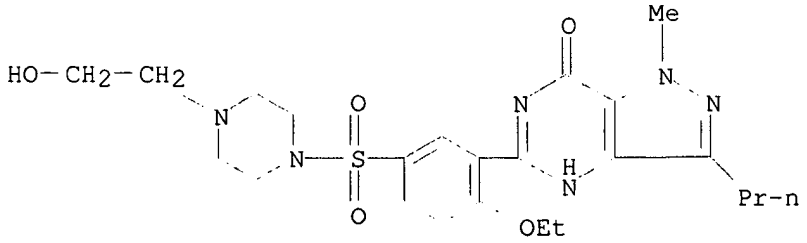
RN 139755-83-2 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



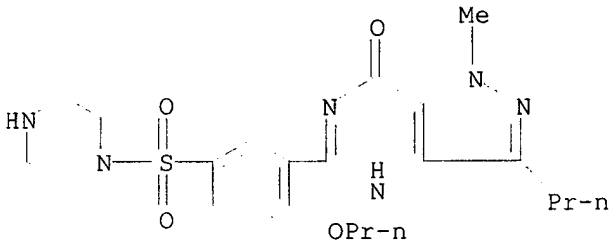
RN 139755-84-3 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-(1-methyl)- (9CI) (CA INDEX NAME)



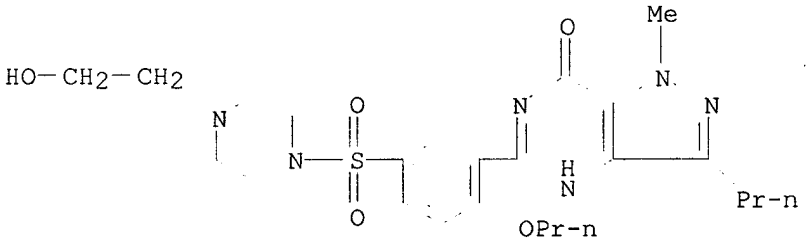
RN 139755-85-4 HCAPLUS
CN 1-Piperazineethanol, 4-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 139755-86-5 HCAPLUS
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 139755-87-6 HCAPLUS
CN 1-Piperazineethanol, 4-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 18:05:02 ON 26 FEB 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

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L95 ANSWER 1 OF 17 USPATFULL
AN 2003:4131 USPATFULL
TI Combination therapy for modulating the human sexual response
IN Podolski, Joseph S., The Woodlands, TX, UNITED STATES
PA ZONAGEN, INC. (U.S. corporation)
PI US 2003004170 A1 20030102
AI US 2002-217575 A1 20020813 (10)
RLI Division of Ser. No. US 2000-403623, filed on 1 Feb 2000, PENDING A 371 of International Ser. No. WO 1998-US10230, filed on 19 May 1998, PENDING
PRAI US 1997-49947P 19970519 (60) <--
DT Utility
FS APPLICATION
LREP Attention: Patent Administrator, KATTEN MUCHIN ZAVIS ROSENMAN, Suite 1600, 525 West Monroe Street, Chicago, IL, 60661-3693
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 927

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention is directed to compositions and methods for modulating the human sexual response. The compositions comprise two or more pharmaceutically active agents which preferably include an alpha-adrenergic antagonist and a phosphodiesterase inhibitor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1997-49947P 19970519 (60) <--
SUMM [0020] **Sildenafil**, (**Viagra**.TM., Pfizer, Inc.) 5-[2-ethoxy-5-(4-methylpiperazine-1-ylsulfonyl)phenyl]-1-methyl-3-proplyl-6,7-dihydro-1-H-pyrazolo[4,3-d]pyrimidin-7-one has also been shown to be useful as an oral treatment for male erectile dysfunction. [Martel et al., **Sildenafil**, Drugs of the Future, 22:138-143 (1997) which is incorporated in its entirety herein by reference.] See also, Boolell et al., Int'l. J. Impot. Res., 8:47-52 (1996) and Boolell et al., Br. J. Urol, 78:257-261 (1996) both of which are incorporated herein in their entirety by reference. **Sildenafil** and related compounds are described in EP 0702555B1, which is incorporated herein by reference, is a phosphodiesterase V inhibitor and more particularly a cyclic GMP-specific phosphodiesterase inhibitor.

SUMM [0022] Typically, the foregoing orally administrable compositions show success rates of less than 100% in treated populations. Results also show that the quality of the sexual response seen in patients, i.e., the relative rigidity of the erections achieved with for example **Sildenafil** is variable. [See, Boolell et al, Br. J. Urol., 78:257-261 (1996).] Therefore, there continues to exist a need in the art for effective compositions and methods for modulating human sexual response and especially for enhancing erectile ability in individuals suffering from erectile dysfunction or for whom the quality of their sexual response is less than satisfactory. Ideally, such means would be convenient and simple to use, would not require a constant dosage regimen or even multiple doses to achieve desired results (i.e., would be available on demand), would be non-invasive, would allow a rapid and predictable capacity to improve sexual responsiveness, and would improve the quality of the sexual response.

SUMM [0024] Another aspect of the present invention is directed to a combination of a first pharmaceutically active agent and a second pharmaceutically active agent wherein the first pharmaceutically active agent is selected from the group consisting of phentolamine, phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine, yohimbine, organic nitrates (e.g. nitroglycerin), thymoxamine, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, and wherein the second pharmaceutically active agent is selected from the group consisting of phosphodiesterase inhibitors or a dopaminergic agonist. The presently preferred first pharmaceutically active agent is phentolamine mesylate. Preferred phosphodiesterase inhibitors include xanthine derivatives, amrinone, Vesnarinone, milrinone, rolipram, RO-1724, 8-methoxymethyl IBMX, cilostamide, Zapranast, MY-5445, M&B 22, 948, phenoximone, Dipyridamole, IBMX, the 5-(2'-alkoxyphenyl)pyrazolo[4,3-d]pyrimidin-7-ones i.e., **Sildenafil**, (**Viagra**.TM.) also referred to as 5-[2-ethoxy-5-(4-methylpiperazine-1-ylsulfonyl) phenyl]-1-methyl-3 propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (see, Drugs of the Future22(2):138-143 (1997)), or 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidine-5-yl) phenylsulphonyl]4-methylpiperazine (see, Boolell et al., Int. J. Impot. Res., 8:47-52 (1996)) and their salts, and papaverine. A preferred dopaminergic agonist useful in the practice of the invention is apomorphine (Pentech Pharmaceuticals).

SUMM [0027] A preferred oral formulation comprises in combination, at least a first and a second pharmaceutically active agent in a rapidly dissolving

orally administrable tablet. Preferred rapidly dissolving tablets have a disintegration time of from about 1 minute to about 10 minutes. Most preferred are rapidly dissolving tablets having the disintegration times of less than one minute. Preferred oral doses of phentolamine mesylate in the formulations of the present invention are preferably from about 5 mg to about 100 mg while preferred, doses of for example, **Sildenafil**, in the same tablet are preferably from about 5 mg to about 150 mg. Preferred doses of papaverine, when used in combination with other pharmaceutically active agents, are 75 mg, 150 mg, and 300 mg.

SUMM [0034] First pharmaceutically active agents useful for manufacturing the medicament include, but are not limited to alpha-adrenergic antagonists. More particularly, the pharmaceutically active agents include phentolamine mesylate, phentolamine hydrochloride, phenoxybenzamine yohimbine, organic nitrates, thymoxamine, imipramine, verapamil, isoxsuprine, naftidrofuryl, tolazoline, atepamezole, deacetylmoxisylyte, delequamine, and salts thereof Other pharmaceutically active agents useful in the compositions of the present invention include phosphodiesterase inhibitors such as but not limited to xanthine derivatives, amrinone, milrinone, rolipram, Vesnarinone, RO-1724, 8-methoxymethyl IBMX, cilostamide, Zapranast, MY-5445, M&B 22, 948, phenoximone, Dipyridamole, IBMX, **Sildenafil** and its **citrate**, and papaverine. Still other pharmaceutically active agents useful in the compositions of the invention include dopaminergic antagonists, for example, apomorphine.

SUMM [0047] Chronic systemic illnesses such as cirrhosis, chronic renal failure, malignancies and other systemic diseases can also cause impotence. Neurogenic impotence arising in the central nervous system can be caused by temporal lobe disorders caused by trauma, epilepsy, neoplasms and stroke, intramedullary spinal lesions, paraplegia, and demyelinating disorders. Neurogenic causes of impotence arising in the peripheral nervous system include somatic or autonomic **neuropathies**, pelvic neoplasms, granulomas, trauma, and others. Urologic causes of impotence include complete prostatectomy, local trauma, neoplasms, Peyronie's disease, and others. In addition, as discussed above, a significant percentage of cases of impotence are vasculogenic in nature.

SUMM [0055] Second pharmaceutically active agents (such as phosphodiesterase inhibitors) useful in the combination of the present invention include phosphodiesterase inhibitors such as (but not limited to) those that inhibit any of the families and/or subtypes of phospodiesterases set out in Beavo et al. In: Advances in Second Messenger and Phosphoprotein Research 22: 1-38 (Greengard et al. Eds., (1988) and others which are known in the art. Exemplary phosphodiesterase inhibitors include xanthine derivatives, amrinone, milrinone, rolipram, Vesnarinone, RO-1724, 8-methoxymethyl IBMX, cilostamide, Zapranast, MY-5445, M&B 22, 948, phenoximone, Dipyridamole, IBMX, the 5-(2'-alkoxyphenyl)pyrazolo[4,3-d]pyrimidin-7-ones and, in particular, **Sildenafil**, and papaverine.

SUMM [0056] Other agents that are useful in combination with the alpha-adrenergic antagonist (e.g., phentolamine) and a phosphodiesterase inhibitor (**Sildenafil**) include .alpha.-adrenoceptor antagonists atipamezole, deacetylmoxisylyte HCl, and delequamine HCl. Other compositions include phentolamine and/or **Sildenafil** in combination with a dopaminergic agonist such as apomorpine.

DETD [0066] Exemplary formulations of a rapidly dissolving tablet that includes phentolamine mesylate and **Sildenafil** are set out below.

TABLE 1

	mg/tablet
Phentolamine Mesylate, USP	40
Sildenafil	50
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	162
Microcrystalline Cellulose, NF	120
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

DETD [0073] Other illustrative formulations are set out below.

TABLE 2

	mg/tablet
Phentolamine Mesylate, USP	20
Sildenafil (**Viagra** .TM.)	50
Silicon Dioxide, NF	8
Stearic Acid, NF	4
Lactose, NF	182
Microcrystalline Cellulose, NF	120
Croscarmellose Sodium, NF	16
Total Tablet Weight	400

DETD [0077] While the studies described above were conducted using a rapidly dissolving formulation (as a preferred embodiment), other formulations that allow rapid absorption of the combination of active agents and corresponding improvement in erectile ability are within the scope of the present invention. For example, the present invention also includes a chewable tablet formulation shown in Table 4.

TABLE 4

	mg/tablet
Phentolamine Mesylate, USP	40
Sildenafil	50
Silicon Dioxide, NF	12
Stearic Acid, NF	12
Lactose, NF	100
Sweetrex	298
Aspartame	40
ProSweet	8
Peppermint Flavor #860-172	40
Total Tablet Weight	600

DETD [0083] Among the phosphodiesterase inhibitors useful in the combinations of the present invention are phosphodiesterase inhibitors such as but not limited to those that inhibit any of the families and/or subtypes of phosphodiesterase isozymes set out in Beavo et al. In: Advances in Second Messenger and Phosphoprotein Research 22: 1-38 (Greengard et al. Eds.)(1988). Exemplary phosphodiesterase inhibitors include xanthine derivatives, amrinone, milrinone, rolipram, Vesnarinone, RO-1724, 8-methoxymethyl IBMX, cilostamide, Zapranast, MY-5445, M&B 22, 948, phenoximone, Dipyridamole, IBMX, **Sildenafil** and papaverine.

DETD [0092] **Sildenafil** has been shown to be effective at various doses including 25 mg and 50 mg (see Boolell et al, Br. J. Urology, 78:257-261 (1996)).

DETD [0093] A preferred embodiment of the invention comprises about 5 mg to about 100 mg phentolamine mesylate in combination with about 5 mg to about 125 mg **Sildenafil**.

DETD [0096] Preferred embodiments of the present invention for use in both males and females involves the administration of from about 5 mg to about 100 mg of phentolamine mesylate and about 5 to about 150 mg **Sildenafil** in a rapidly dissolving oral formulation of the present invention from about 1 minute to about 1 hour prior to, and in preparation for intercourse.

DETD [0104] Papaverine, a known non-specific phosphodiesterase inhibitor, in combination with phentolamine mesylate was compounded in a rapidly dissolving formulation as set out in Table 5 except that papaverine at the doses indicated below was substituted for **Sildenafil**. Dosages were as follows:

TABLE 5

mg/tablet

Phentolamine Mesylate, (alone)	40
Papaverine (alone)	150
Phentolamine Mesylate plus	40
Papaverine	75
Phentolamine Mesylate plus	40
Papaverine	150
Phentolamine Mesylate plus	40
Papaverine	300

CLM What is claimed is:

4. The composition of claim 3 wherein the type V cyclic GMP-specific phosphodiesterase inhibitor is 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo [4,3d]pyrimidin-5-yl) phenylsulfonyl]-4-methyl piperazine (**Sildenafil**).

5. A composition comprising from about 5 mg to about 100 mg phentolamine and from about 5 mg to about 150 mg 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3d]pyrimidin-5-yl) phenylsulfonyl]-4-methyl piperazine (**Sildenafil**) and a pharmaceutically acceptable carrier.

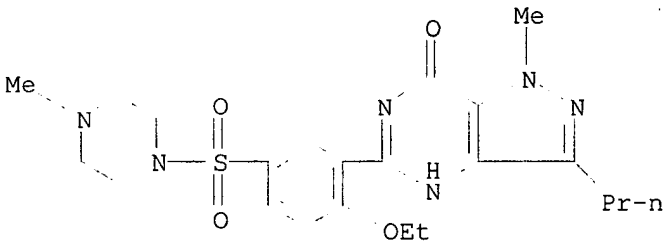
6. A composition comprising from about 5 mg to about 100 mg phentolamine and from about 5 mg to about 150 mg 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7oxo-3-propyl-1H-pyrazolo[4,3 [d]pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine (**Sildenafil**) in an orally administrable tablet, the tablet having a disintegration time of less than about twenty minutes.

IT 50-60-2, Phentolamine 58-00-4, Apomorphine 58-74-2, Papaverine 65-28-1, Phentolamine mesylate 73-05-2, Phentolamine hydrochloride 37221-79-7, Vasoactive intestinal peptide **139755-83-2**, Sildenafil
(combination therapy for modulating human sexual response)

IT **139755-83-2**, Sildenafil
(combination therapy for modulating human sexual response)

RN 139755-83-2 USPATFULL

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



L95 ANSWER 2 OF 17 USPATFULL
AN 2002:323200 USPATFULL
TI Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors
IN Du Bois, Daisy Joe, Palo Alto, CA, UNITED STATES
PI US 2002183369 A1 20021205
AI US 2002-117370 A1 20020405 (10)
RLI Division of Ser. No. US 2000-670759, filed on 27 Sep 2000, GRANTED, Pat. No. US 6399601
PRAI US 1999-157148P 19990930 (60) <--
DT Utility
FS APPLICATION
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4347
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds of Formula I ##STR1##

or stereoisomers, pharmaceutically acceptable salts or prodrugs thereof or a pharmaceutically acceptable salts of the prodrugs. This invention also relates to pharmaceutical compositions comprising a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-157148P 19990930 (60) <--
AB or stereoisomers, pharmaceutically acceptable salts or prodrugs thereof or a pharmaceutically acceptable salts of the prodrugs. This invention also relates to pharmaceutical compositions comprising a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.
SUMM [0002] This invention relates to bicyclic pyrrolyl amides and pharmaceutical compositions comprising bicyclic pyrrolyl amides. This invention also relates to the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, and tissue ischemia, particularly myocardial ischemia, using the bicyclic pyrrolyl amides.

SUMM [0072] Also provided are methods of treating diabetic **neuropathy**, the methods comprising the step of administering to a patient having

diabetic **neuropathy** a therapeutically effective amount of a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs.

SUMM [0139] Also provided are kits for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts in a patient having diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts, the kits comprising:

SUMM [0141] b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts; and

SUMM [0165] Also provided are kits for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia in a patient having diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the kits comprising:

SUMM [0167] b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia; and

SUMM [0169] Also provided are methods of treating diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the method comprising the step of administering to a patient having diabetes, insulin resistance, diabetic **neuropathy** , diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, a therapeutically effective amount of a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs in combination with at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM [0170] Also provided are pharmaceutical compositions comprising a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs and at least one additional compound useful to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM [0171] The present invention relates to compounds of Formula I, stereoisomers of compounds of Formula I, pharmaceutically acceptable salts of compounds of Formula I, prodrugs of compounds of Formula I, and pharmaceutically acceptable salts of the prodrugs of compounds of

Formula I. The invention also relates to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, and tissue ischemia, particularly myocardial ischemia, and to pharmaceutically acceptable compositions comprising a compound of Formula I, stereoisomers of compounds of Formula I, pharmaceutically acceptable salts of compounds of Formula I, prodrugs of compounds of Formula I, and pharmaceutically acceptable salts of the prodrugs of compounds of Formula I.

SUMM [0202] A patient in need of glycogen phosphorylase inhibition is a patient having a disease or condition in which glycogen phosphorylase plays a role in the disease of condition. Examples of patients in need of glycogen phoshphorylase inhibition include patients having diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance, and the diabetic complications, such a nephropathy, retinopathy, **neuropathy** and cataracts), hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and tissue ischemia.

SUMM [0250] In another aspect, the present invention concerns the treatment of diabetes, including impaired glucose tolerance, insulin resistance, insulin dependent diabetes mellitus (Type I) and non-insulin dependent diabetes mellitus (NIDDM or Type II). Also included in the treatment of diabetes are the treatment of the diabetic complications, such as **neuropathy**, nephropathy, retinopathy or cataracts.

SUMM [0251] Diabetes can be treated by administering to a patient having diabetes (Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as **neuropathy**, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention. It is also contemplated that diabetes be treated by administering a compound of the present invention or an other glycogen phosphorylase inhibitor in combination with an additional agent that can be used to treat diabetes and/or obesity. Preferred gylcogen phosphorylase inhibitors that are useful in combination with other agents useful to treat diabetes and/or obesity include those of Formula I. Additional preferred gylcogen phosphorylase inhibitors are disclsoed in PCT publications WO 96/39384 and WO 96/39385.

SUMM [0252] Representative agents that can be used to treat diabetes include insulin and insulin analogs: (e.g., LysPro insulin. inhaled formulations comprising insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH.sub.2; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; (.alpha.2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, insulinotropin, exendin-4, BTS-67582, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; RXR agonists: JTT-501, MCC-555, MX-6054, DRF2593,GI-262570, KRP-297, LG100268; fatty acid oxidation inhibitors: clomoxir, etomoxir; .alpha.-glucosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; .beta.-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: **sildenafil**, L686398: L-386,398; lipid-lowering agents: benfluorex, atorvastatin; antiobesity agents: fenfluramine, orlistat, sibutramine; vanadate and vanadium complexes (e.g., Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists: pramlintide, AC-137;

lipoxygenase inhibitors: masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1 B inhibitors: L-783281, TER1 7411, TER17529; gluconeogenesis inhibitors: GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase kinase inhibitors: lithium chloride, CT98014, CT98023; galanin receptor agonisnts; MTP inhibitors such as those disclosed in U.S. provisional patent application number 60/164,803; growth hormone secretagogues such as those disclosed in PCT publication numbers WO 97/24369 and WO 98/58947; NPY antagonists: PD-160170, BW-383, BW1229, CGP-71683A, NGD 95-1, L-152804; Anorectic agents inlcuding 5-HT and 5-HT2C receptor antagonists and/or mimetics: dexfenfluramine, Prozac.RTM., Zoloft.RTM.; CCK receptor agonists: SR-27897B; galanin receptor antagonists; MCR-4 antagonists: HP-228; leptin or mimetics: leptin; 11-beta-hydroxysteroid dehydrogenase type-I inhibitors; urocortin mimetics, CRF antagonists, and CRF binding proteins: RU-486, urocortin. Other anti-diabetic agents that can be used in combination with a glycogen phosphorylase inhibitor include ergoset and D-chiroinositol. Any combination of agents can be administered as described above.

SUMM [0253] In addition to the categories and compounds mentioned above, gylcogen phosphorylase inhibitors, preferrably the compounds of the present invention, can be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol dehydrogenase inhibitors, or combinations thereof, to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, particularly myocardial ischemia.

SUMM [0255] Each of the thyromimetic compounds referenced above and other thyromimetic compounds can be used in combination with the compounds of the present invention to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM [0256] The compounds of the present invention can also be used in combination with aldose reductase inhibitors. Aldose reductase inhibitors constitute a class of compounds that have become widely known for their utility in preventing and treating conditions arising from complications of diabetes, such as diabetic **neuropathy** and nephropathy. Such compounds are well known to those skilled in the art and are readily identified by standard biological tests. For example, the aldose reductase inhibitors zopolrestat, 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-, and related compounds are described in U.S. Pat. No. 4,939,140 to Larson et al.

SUMM [0301] Each of the aldose reductase inhibitors referenced above and other aldose reductase inhibitors can be used in combination with the compounds of the present invention to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM [0345] The compounds of the present invention can also be used in combination with sorbitol dehydrogenase inhibitors. Sorbitol dehydrogenase inhibitors lower fructose levels and have been used to

treat or prevent diabetic complications such as **neuropathy**, retinopathy, nephropathy, cardiomyopathy, microangiopathy, and macroangiopathy. U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

SUMM [0346] Each of the sorbitol dehydrogenase inhibitors referenced above and other sorbitol dehydrogenase inhibitors can be used in combination with the compounds of the present invention to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM [0357] Each of the NHE-1 inhibitors referenced above and other NHE-1 inhibitors can be used in combination with the compounds of the present invention to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

CLM What is claimed is:
8. A method of treating or preventing atherosclerosis, diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperglycemia, hypertension, tissue ischemia, or myocardial ischemia, the method comprising the step of administering to a patient having or at risk of having atherosclerosis, diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperglycemia, hypertension, tissue ischemia, or myocardial ischemia a therapeutically effective amount of a compound of claim 1, a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug.

11. A kit for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia in a patient having diabetes, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the kit comprising: a) a first pharmaceutical composition comprising a compound in accordance with claim 1, or a stereoisomer, pharmaceutically acceptable salt or prodrug of the compound, or a pharmaceutically acceptable salt of the prodrug; b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia; and c) a container for containing the first and second compositions.

12. A method of treating diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the method comprising the step of administering to a patient having diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, a therapeutically effective amount of a compound of claim 1, a stereoisomer, pharmaceutically acceptable

salt or prodrug thereof, or a pharmaceutically acceptable salt of a prodrug in combination with at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

13. A pharmaceutical composition comprising a compound of claim 1, a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug and at least one additional compound useful to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

IT **Nerve, disease**
(diabetic neuropathy, treatment; prepn. of bicyclic pyrrolylcarboxamides as glycogen phosphorylase inhibitors)

L95 ANSWER 3 OF 17 USPATFULL
AN 2002:301556 USPATFULL
TI Treatment of sexual dysfunction
IN Gonzalez, Maria Isabel, Cambridge, UNITED KINGDOM
Higginbottom, Michael, Cambridge, UNITED KINGDOM
Stock, Herman Thijs, Wijchen, NETHERLANDS
Pritchard, Martyn Clive, Huntingdon, UNITED KINGDOM
Pinnock, Robert Denham, Cambridgshire, UNITED KINGDOM
Van Der Graaf, Pieter Hadewijn, Kent, UNITED KINGDOM
Naylor, Alisdair Mark, Kent, UNITED KINGDOM
Wayman, Christopher Peter, Kent, UNITED KINGDOM
PI US 2002169101 A1 20021114
AI US 2001-999284 A1 20011115 (9)
RLI Continuation-in-part of Ser. No. US 2001-759777, filed on 12 Jan 2001, PENDING Continuation-in-part of Ser. No. US 2000-700165, filed on 9 Nov 2000, PENDING A 371 of International Ser. No. WO 2000-GB1787, filed on 10 May 2000, UNKNOWN
PRAI GB 2001-9910 20010423
GB 2001-11037 20010504
US 1999-133355P 19990510 (60) <--
DT Utility
FS APPLICATION
LREP WARNER-LAMBERT COMPANY, 2800 PLYMOUTH ROAD, ANN ARBOR, MI, 48107
CLMN Number of Claims: 67
ECL Exemplary Claim: 1
DRWN 24 Drawing Page(s)
LN.CNT 5522
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Bombesin receptor antagonists have been found to be useful in the treatment of sexual dysfunction in both males and females. They may be selective BB1 antagonists or mixed BB1/BB2 antagonists. Combinations are disclosed of bombesin receptor antagonists with a range of other active compounds, for example PDE5 inhibitors, NEP inhibitors and lasofoxifene.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-133355P 19990510 (60) <--
SUMM [0004] In males, impotence can be defined as an inability to achieve penile erection or ejaculation. Its prevalence is claimed to be between 2% and 7% of the human male population, increasing with age up to 50 years and between 18% and 80% between 55 and 80 years of age. In the USA alone, for example, it has been estimated that there are up to 10 million impotent males, with the majority suffering from problems of organic rather than of psychogenic origin. Although many different drugs

have been shown to induce penile erection, they were only effective after direct injection into the penis e.g. intraurethrally or intracavernosally (i.c.) and were not approved for erectile dysfunction. U.S. Pat. No. 5,576,290 discloses peptides which are stated to induce erection, but they have to be given subcutaneously e.g. by injection, and if an excessive dose is given they produce an exaggerated erectile response and stomach discomfort. Impotence treatment was revolutionized by the unexpected discovery that cGMP PDE inhibitors, e.g. pyrazolo[4,3-d]pyrimidin-7-ones were useful in the treatment of erectile dysfunction and could be administered orally, therefore obviating the disadvantages associated with i.c. administration. One such compound that is currently being manufactured is **sildenafil** (**Viagra**).

DETD [0086] (ii) Neurogenic etiologies such as spinal cord injuries or diseases of the central nervous system including multiple sclerosis, diabetes, Parkinsonism, cerebrovascular accidents, peripheral **neuropathies**, trauma or radical pelvic surgery.

DETD [0103] (ii) Neurogenic etiologies such as spinal cord injuries or diseases of the central nervous system including multiple sclerosis, diabetes, Parkinsonism, cerebrovascular accidents, peripheral **neuropathies**, trauma or radical pelvic surgery.

DETD [0401] Vasodilators for the treatment of sexual dysfunctions of organic (rather than psychogenic) origin, act at the penis, clitoris or vagina level on local blood flow or lubricant secretions. Vasodilators useful for the treatment of sexual dysfunction include alprostadil or phentolamine, NO (nitric oxide) enhancers such as L-arginine, and PDE5 inhibitors such as **sildenafil** or a pharmaceutically acceptable salt thereof (Scrip's Complete Guide to Women's Healthcare, p.194-205, 2000)(Sachs B. D., 2000, Benet and Melman, 1995), VIP (Vaso Intestinal Peptide) enhancers (Scrip's Complete Guide to Women's Healthcare, p.194-205, 2000) or angiotensin-2 receptor antagonists such as losartan (American Heart Association meeting, New Orleans, 2000).

DETD [0460] 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**sildenafil**) also known as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methylpiperazine (see EP-A-0463756);

DETD [1062] Berman, J., Goldstein, I., Werbin, T. et al. (1999a). Double blind placebo controlled study with crossover to assess effect of **sildenafil** on physiological parameters of the female sexual response. J. Urol., 161, 805.

L95 ANSWER 4 OF 17 USPATFULL
AN 2002:259449 USPATFULL
TI Biphenyl sulfonamides as dual angiotensin endothelin receptor antagonists
IN Murugesan, Natesan, Princeton Junction, NJ, UNITED STATES
Tellew, John E., Pennington, NJ, UNITED STATES
Macor, Jhon E., Flemington, NJ, UNITED STATES
Gu, Zhengxiang, Princeton, NJ, UNITED STATES
PI US 2002143024 A1 20021003
AI US 2000-737201 A1 20001214 (9)
RLI Continuation-in-part of Ser. No. US 2000-643640, filed on 22 Aug 2000, ABANDONED Continuation-in-part of Ser. No. US 2000-604322, filed on 26 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2000-513779, filed on 25 Feb 2000, PENDING Continuation-in-part of Ser. No. US 2000-481197, filed on 11 Jan 2000, ABANDONED Continuation-in-part of Ser. No. US 1999-464037, filed on 15 Dec 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-345392, filed on 1 Jul 1999, ABANDONED
PRAI US 1998-91847P 19980706 (60) <--
DT Utility
FS APPLICATION

LREP MARLA J MATHIAS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000
CLMN Number of Claims: 108
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 8673
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel biphenyl sulfonamide compounds which are combined angiotensin and endothelin receptor antagonists are claimed along with methods of using such compounds in the treatment of conditions such as hypertension and other diseases, as well as pharmaceutical compositions containing such compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1998-91847P 19980706 (60) <--
SUMM [0207] In addition, the compounds of this invention are also useful as anti-arrhythmic agents; anti-anginal agents; anti-fibrillatory agents; anti-asthmatic agents; anti-atherosclerotic and anti-arteriosclerotic agents (including anti-transplantation arteriosclerotic agents); additives to cardioplegic solutions for cardiopulmonary bypasses; adjuncts to thrombolytic therapy; and anti-diarrheal agents. The compounds of this invention may be useful in therapy for myocardial infarction; therapy for peripheral vascular disease (e.g., Raynaud's disease, intermittent claudication and Takayashu's disease); treatment of cardiac hypertrophy (e.g., hypertrophic cardiomyopathy); treatment of primary pulmonary hypertension (e.g., plexogenic, embolic) in adults and in the newborn and pulmonary hypertension secondary to heart failure, radiation and chemotherapeutic injury, or other trauma; treatment of central nervous system vascular disorders, such as stroke, migraine and subarachnoid hemorrhage; treatment of central nervous system behavioral disorders; treatment of gastrointestinal diseases such as ulcerative colitis, Crohn's disease, gastric mucosal damage, ulcer, inflammatory bowel disease and ischemic bowel disease; treatment of gall bladder or bile duct-based diseases such as cholangitis; treatment of pancreatitis; regulation of cell growth; treatment of benign prostatic hypertrophy; restenosis following angioplasty or following any procedure including transplantation and stenting; therapy for congestive heart failure including inhibition of fibrosis; inhibition of left ventricular dilatation, remodeling and dysfunction; and treatment of hepatotoxicity and sudden death. The compounds of this invention are useful in the treatment of sickle cell disease including the initiation and/or evolution of the pain crises of this disease; treatment of the deleterious consequences of ET-producing tumors such as hypertension resulting from hemangiopericytoma; treatment of early and advanced liver disease and injury including attendant complications (e.g., hepatotoxicity, fibrosis and cirrhosis); treatment of spastic diseases of the urinary tract and/or bladder; treatment of hepatorenal syndrome; treatment of immunological diseases involving vasculitis such as lupus, systemic sclerosis, mixed cryoglobulinemia; and treatment of fibrosis associated with renal dysfunction and hepatotoxicity. The compounds of this invention are useful in therapy for metabolic and neurological disorders; cancer; insulin-dependent and non insulin-dependent diabetes mellitus; **neuropathy**; retinopathy; epilepsy; hemorrhagic and ischemic stroke; bone remodeling; psoriasis; and chronic inflammatory diseases such as arthritis, rheumatoid arthritis, osteoarthritis, sarcoidosis and eczematous dermatitis (all types of dermatitis).

SUMM [0221] The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of endothelin-dependent or angiotensin II-dependent disorders. For example, the compounds of this invention can be formulated in combination with endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; thromboxane receptor antagonists

such as ifetroban; potassium channel openers; thrombin inhibitors (e.g., hirudin and the like); growth factor inhibitors such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents such as GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants such as warfarin, low molecular weight heparins such as enoxaparin, Factor VIIa inhibitors, and Factor Xa inhibitors such as those described in U.S. Ser. No. 09/496,571 filed Feb. 2, 2000 (attorney docket HA 723); renin inhibitors; angiotensin converting enzyme (ACE) inhibitors such as captopril, zofenopril, fosinopril, ceranapril, alacepril, enalapril, delapril, pentopril, quinapril, ramipril, lisinopril and salts of such compounds; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants such as questran; niacin; anti-atherosclerotic agents such as ACAT inhibitors; MTP inhibitors such as those described in U.S. Ser. No. 09/007,938 filed Jan. 16, 1998 (attorney docket HX 91); calcium channel blockers such as amlodipine besylate; potassium channel activators; alpha-adrenergic agents, beta-adrenergic agents such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide or benzothiazide as well as ethacrynic acid, tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, amiloride and spironolactone and salts of such compounds; thrombolytic agents such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase and anisoylated plasminogen streptokinase activator complex (APSAC); anti-diabetic agents such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, and glipizide), biguanide/glyburide combinations such as those described in U.S. Ser. No. 09/432,465 filed Nov. 3, 1999 (attorney docket LA 46) and U.S. Ser. No. 09/460,920 filed Dec. 14, 1999 (attorney docket LA 46a); thiozolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists such as spironolactone and eplerenone; growth hormone secretagogues such as those described in U.S. Ser. No. 09/417,180 filed Oct. 12, 1999 (attorney docket LA 25) and U.S. Ser. No. 09/506,749 filed Feb. 18, 2000 (attorney docket LA 26); aP2 inhibitors such as those described in U.S. Ser. No. 09/391,053 filed Sep. 7, 1999 (attorney docket LA 24a) and U.S. Ser. No. 09/390,275 filed Sep. 7, 1999 (attorney docket LA 24b); digitalis; ouabian; non-steroidal antiinflammatory drugs (NSAIDS) such as aspirin and ibuprofen; phosphodiesterase inhibitors such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., **sildenafil**); protein tyrosine kinase inhibitors; antiinflammatories; antiproliferatives such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate and mofetil; chemotherapeutic agents; immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes); antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone anatagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as paclitaxel

(Taxol.RTM.), docetaxel (Taxotere.RTM.), and epothilones A-F or their analogs or derivatives; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin); cyclosporins; steroids such as prednisone or dexamethasone; gold compounds; cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-alpha inhibitors such as tenidap; anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel) rapamycin (sirolimus or Rapamune), leflunimide (Arava); and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx).

L95 ANSWER 5 OF 17 USPATFULL
AN 2002:221831 USPATFULL
TI Methods and compositions for treating diseases and conditions of the eye
IN Laties, Alan M., Philadelphia, PA, UNITED STATES
PI US 2002119974 A1 20020829
AI US 2002-126375 A1 20020419 (10)
RLI Continuation of Ser. No. US 2000-607562, filed on 29 Jun 2000, ABANDONED
PRAI US 1999-146095P 19990728 (60) <--
DT Utility
FS APPLICATION
LREP Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340
CLMN Number of Claims: 51
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 964
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for the prevention and treatment of diseases and conditions of the eye including, but are not limited to: central retinal artery occlusion; central retinal vein occlusion; optic **neuropathy** including, but not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**; and macular (dry) degeneration are disclosed. These methods comprise administering to a patient a prophylactically or therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor. Pharmaceutical compositions and dosage forms comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-146095P 19990728 (60) <--
AB Methods for the prevention and treatment of diseases and conditions of the eye including, but are not limited to: central retinal artery occlusion; central retinal vein occlusion; optic **neuropathy** including, but not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**; and macular (dry) degeneration are disclosed. These methods comprise administering to a patient a prophylactically or therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor. Pharmaceutical compositions and dosage forms comprising cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors are also disclosed.
SUMM [0002] This invention relates to methods of using, and compositions comprising, cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitors. The methods and compositions of the invention are useful in the prevention and treatment of diseases and conditions of the eye including, but not limited to, central retinal artery occlusion, central retinal vein occlusion, optic **neuropathy** including anterior ischemic optic **neuropathy** and glaucomatous optic

neuropathy, and macular (dry) degeneration.

SUMM [0004] An optic **neuropathy** (i.e., a disease or damage of the optic nerve) underlies the loss of vision characteristic of several forms of glaucoma. It is widely accepted that glaucomatous optic **neuropathy** is usually caused by unacceptably high intraocular pressure (IOP). The upper limit of normal human IOP, which depends on the inflow and outflow of aqueous humor, is variously defined to be about 20 to about 22 mm Hg above atmospheric pressure. Cioffi, G. A. and Van Buskirk, E. M., Textbook of Ophthalmology, Wright, K. W. ed., p. 563 (Williams & Wilkins, 1997). Current methods of treating glaucoma are thus directed at decreasing IOP. The Merck Manual 735-736 (17.sup.th ed. 1999). Drugs currently used for the treatment of glaucoma either increase outflow or decrease inflow of the aqueous humour. See, e.g., Physicians' Desk Reference for Ophthalmology 10-12 (27.sup.th ed. 1999).

SUMM [0005] Although high IOP reportedly causes most cases of glaucomatous optic **neuropathy**, an inadequate supply of blood to the optic nerve reportedly causes glaucomatous optic **neuropathy** in some cases. The Merck Manual 734 (17.sup.th ed. 1999); see also, Delaey, C. and Van de Voorde, J., Invest. Ophthal. & Vis. Scd. 39(9):1642-1646 (1998). Despite such reports, the approximately one-third of patients with open-angle glaucoma who have pressures in a normal range are treated with agents that lower IOP. Unfortunately, in cases wherein glaucomatous optic **neuropathy** results from insufficient vascular nourishment (i.e., vascular malnourishment) of the optic nerve, reduction of IOP can have inadequate therapeutic effect.

SUMM [0006] It has recently been reported that the systemic administration of a nitric oxide (NO) donor can slow the progression of glaucomatous optic **neuropathy**. See, e.g., Afshari, N. A., et al., Invest Ophthalmol. Vis. Sci. 38(Suppl.):S277 (1997). At least two explanations have been proposed for this observation, both of which are based on the ability of nitric oxide (NO) to activate the enzyme guanylate cyclase and thereby increase levels of cyclic guanosine monophosphate (cGMP), a compound which induces the relaxation of smooth muscle cells.

SUMM [0008] It has also been postulated that NO can slow the progression of glaucomatous optic **neuropathy** by inducing dilation of blood vessels in the eye. This theory is supported by a recent report that the administration of the NO donor 5-isosorbide mononitrate increases blood flow to the optic nerve head in humans. Grunwald, J. E., et al., British J. Ophthal. 83(2):162-167 (1999). The authors of that research proposed that the vasodilatation caused by NO can improve perfusion of the optic nerve. At the same time, however, they noted that NO is known to have a neurotoxic potential, and that there is concern that increased NO synthase immunoreactivity at the optic nerve head may actually correlate with disease progression in glaucoma. Id.; see also, Goldstein, I. M., et al., Vision Res. 36(18):2979-2994 (1996), and Neufeld, A. H., et al., Arch Ophthalmol. 115:397-503 (1997).

SUMM [0009] In sum, research has suggested that while administration of NO can slow the progress of glaucomatous optic **neuropathy**, it may not always be safe. A safe and effective method of treating or preventing diseases and conditions of the eye such as glaucomatous optic **neuropathy** is thus desired. Such a method preferably allows treatment of ischemic conditions, wherein damage, blockage, or constriction of a blood vessel to the eye has or will occur.

SUMM [0010] U.S. Pat. No. 5,250,534 discloses a class of cyclic guanosine 3',5'-monophosphate (cGMP) phosphodiesterase type 5 (PDE5) inhibitors potentially useful in the treatment of, for example, conditions of reduced blood vessel patency and glaucoma. One member of this class is

sildenafil, which has two chemical names: 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d[pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine and 5-[2-ethoxy-5-(4-methylpiperazinylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. **Sildenafil citrate** is sold under the tradename **Viagra**.RTM. by Pfizer Inc. and is indicated for the treatment of erectile dysfunction. Physicians' Desk Reference 2424-2426 (53.sup.rd ed. 1999). By slowing the rate of cGMP breakdown, **sildenafil** enhances the vasodilatory effect of naturally produced NO.

SUMM [0011] This invention is directed to novel methods and compositions for treating and preventing acute, sub-acute, and chronic diseases and conditions of the eye. Examples of acute, sub-acute, and chronic diseases and conditions of the eye include, but are not limited to: central retinal or posterior ciliary artery occlusion; central retinal vein occlusion; optic **neuropathy** including, but not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**; and macular (dry) degeneration.

SUMM [0014] A third embodiment of the invention encompasses a method of treating or preventing optic **neuropathy** which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor.

SUMM [0015] Patients in need of treatment or prevention of optic **neuropathy** include, but are not limited to: patients with elevated intraocular pressure; patients greater than about 50 years of age; patients with family histories of optic **neuropathy**; patients with hypertension; patients with diabetes; patients with family histories of diabetes or heart disease; patients who have used, or are currently using, corticosteroids that raise intraocular pressure; and patients who have undergone intraocular surgery.

SUMM [0016] A specific method encompassed by this embodiment is a method of treating or preventing optic **neuropathy** without affecting the intraocular pressure of a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor.

SUMM [0017] Specific types of optic **neuropathy** that can be treated or prevented by methods encompassed by this embodiment include, but are not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**. Glaucomatous optic **neuropathy** can be caused by or associated with an acute, sub-acute, or chronic glaucoma selected from the group consisting of: chronic (idiopathic) open-angle glaucomas; pupillary block glaucomas such as acute angle-closure glaucoma, subacute angle-closure glaucoma, chronic angle-closure glaucoma, and combined-mechanism glaucoma; developmental glaucomas such as congential glaucoma, juvenile glaucoma, Axenfeld-Rieger syndrome, Peters' anomaly, and Aniridia; glaucomas associated with other ocular disorders such as disorders of the corneal endothelium, disorders of the iris and ciliary body, disorders of the lens, disorders of the retina, choroid, and vitreous, and intraocular tumors; glaucomas associated with elevated episcleral venous pressure such as systemic diseases with associated elevated intraocular pressure and glaucoma and corticosteroid-induced glaucoma; glaucomas associated with inflammation and trauma such as keratitis, episcleritis, scleritis, uveitis, ocular trauma, and hemorrhage; glaucomas following intraocular surgery such as ciliary block (malignant) glaucoma, glaucomas in aphakia and pseudoakia, epithelial, fibrous, and endothelial proliferation,

glaucomas associated with corneal surgery, and glaucomas associated with vitreoretinal surgery; and low-tension glaucoma. Preferably, the acute, sub-acute, or chronic glaucoma is selected from the group consisting of: glaucomas associated with elevated episcleral venous pressure; glaucomas associated with inflammation and trauma; glaucomas following intraocular surgery; and low-tension glaucoma.

SUMM [0043] As used herein, the terms "treating optic **neuropathy**" and "treatment of optic **neuropathy**" mean reversing, slowing, or preventing the advancement of optic nerve damage or disease. Symptoms of optic **neuropathy** usually include measurable loss of vision, which is often best noted by evaluation of the visual field.

SUMM [0048] This invention is based on the unexpected discovery that cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 (cGMP PDE5) inhibitors such as compounds of Formula 1 may be used to prevent and/or treat diseases or disorders of the eye. The invention is thus directed to methods and compositions for the treatment or prevention of acute, sub-acute, or chronic diseases or disorders of the eye including, but are not limited to: central retinal artery occlusion; central retinal vein occlusion; optic **neuropathy** including, but not limited to, anterior ischemic optic **neuropathy** and glaucomatous optic **neuropathy**; and macular (dry) degeneration. The invention is further directed to methods and compositions that allow the treatment and/or prevention of diseases or conditions of the eye without significantly affecting intraocular pressure (IOP). These methods are of particular importance in the treatment or prevention of diseases or disorders of the eyes of patients with normal or low IOP.

DETD [0073] Effects of the compounds of the invention on blood flow to the optic nerve are preferably determined using laser doppler flowmetry (LDF), which can measure blood flow in the optic nerve head (ONFlow) and choroid (ChFlow). A study of the effects of orally administered **sildenafil citrate** on ONFlow is as follows.

DETD [0079] In a double-masked, randomized, cross-over design, each subject receives orally either 50 mg of **sildenafil citrate** or placebo. ChFlow and ONFlow are determined monocularly at baseline and one hour after dosing. Additional measurements at two, three, and four hours can also be obtained. Mean arterial blood pressure, heart rate and intraocular pressure are monitored, and ocular perfusion pressure is estimated using known techniques. Determination of ONVel, ONVol, ONFlow, ChVel, ChVol, and ChFlow are performed by one trained examiner, masked with regard to treatment regimen. Results are expressed as mean percentage variations from baseline (.+-.SEM). Normal distribution of the data is assessed with the Wilk-Shapiro test. Statistical evaluation of the results is performed using two-tailed, paired Student*s t-test, linear regression, and correlation analysis. Probability values <0.05 are considered statistically significant.

CLM What is claimed is:

21. A method of treating or preventing optic **neuropathy** which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type 5 inhibitor.

22. The method of claim 21 wherein the patient is selected from the group consisting of: patients with elevated intraocular pressure; patients greater than about 50 years of age; patients with family histories of optic **neuropathy**; patients with hypertension; patients with diabetes; patients with family histories of diabetes or heart disease; patients who have used, or are currently using, corticosteroids that raise intraocular pressure; and patients who have undergone intraocular surgery.

23. The method of claim 21 wherein said treating or preventing optic **neuropathy** does not affect the intraocular pressure of a patient.

24. The method of claim 21 wherein the optic **neuropathy** is anterior ischemic optic **neuropathy**.

25. The method of claim 21 wherein the optic **neuropathy** is glaucomatous optic **neuropathy**.

26. The method of claim 25 wherein the glaucomatous optic **neuropathy** is caused by or associated with an acute, sub-acute, or chronic glaucoma selected from the group consisting of: chronic (idiopathic) open-angle glaucomas; pupillary block glaucomas; developmental glaucomas; glaucomas associated with other ocular disorders; glaucomas associated with elevated episcleral venous pressure; glaucomas associated with inflammation and; glaucomas following intraocular surgery; and low-tension glaucoma.

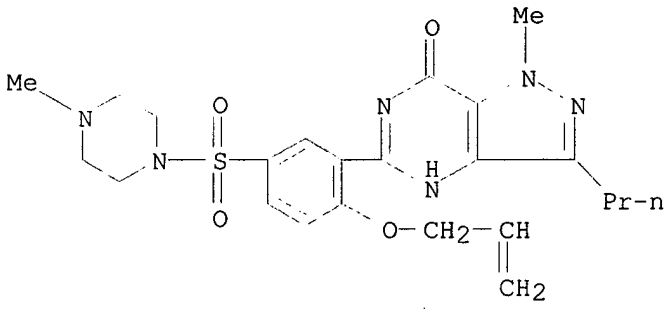
IT **Nerve, disease**
(neuropathy, optic; phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT **139755-81-0 139755-82-1 139755-83-2 139755-84-3 139755-85-4 139755-86-5 139755-87-6**
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

IT **139755-81-0 139755-82-1 139755-83-2 139755-84-3 139755-85-4 139755-86-5 139755-87-6**
(phosphodiesterase type 5 inhibitors for prophylactic and treatment of eye diseases)

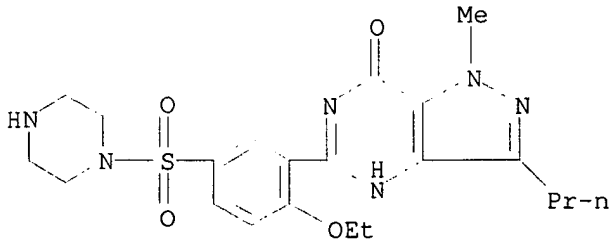
RN 139755-81-0 USPATFULL

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-(2-propenyloxy)phenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)

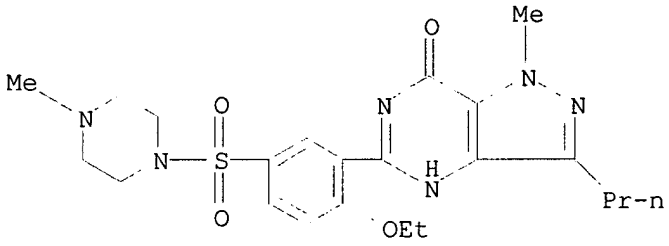


RN 139755-82-1 USPATFULL

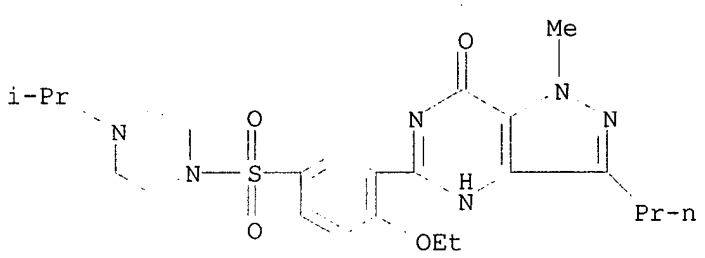
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



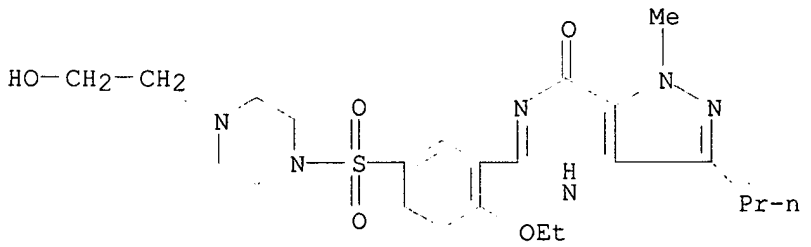
RN 139755-83-2 USPATFULL
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



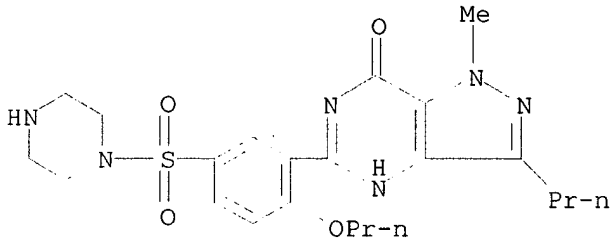
RN 139755-84-3 USPATFULL
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-(1-methyl)- (9CI) (CA INDEX NAME)



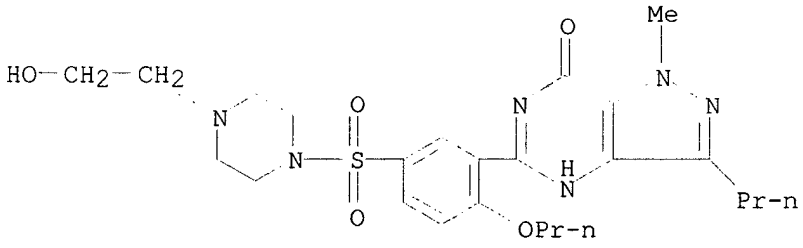
RN 139755-85-4 USPATFULL
CN 1-Piperazineethanol, 4-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 139755-86-5 USPATFULL
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 139755-87-6 USPATFULL
CN 1-Piperazineethanol, 4-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-propoxyphenyl]sulfonyl]- (9CI) (CA INDEX NAME)



L95 ANSWER 6 OF 17 USPATFULL
AN 2002:209572 USPATFULL
TI Endogenous nitric oxide synthesis under conditions of low oxygen tension
IN de Tejada, Inigo Saenz, Madrid, SPAIN
PA NitroMed, Inc., Bedford, MA, United States (U.S. corporation)
PI US 6436997 B1 20020820
AI US 1999-429020 19991029 (9)
RLI Continuation-in-part of Ser. No. WO 1999-US11876, filed on 1 Jun 1999
Continuation-in-part of Ser. No. US 1999-321584, filed on 28 May 1999, now patented, Pat. No. US 6277884
PRAI US 1998-87556P 19980601 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Hale and Dorr LLP
CLMN Number of Claims: 49
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 21 Drawing Page(s)
LN.CNT 1586
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods of promoting synthesis of nitric oxide or endothelium-derived relaxing factor (EDRF) in hypoxic mammalian tissues by administering at least one N-hydroxyguanidine compound that is a substrate of nitric oxide synthase, and, optionally, one or more vasoactive agents and/or thromboxane A2 receptor antagonists. The present invention also provides methods of promoting vasorelaxation and treating sexual dysfunctions in patients by administering at least one N-hydroxyguanidine compound that is a substrate for nitric oxide synthase, and, optionally, at least one vasoactive agent and/or

thromboxane A2 receptor antagonist. The present invention also provides methods for treating clinical conditions resulting from hypoxic conditions such as pulmonary disease, cardiovascular disorders, circulatory hypoxia, specific organ hypoxia, localized hypoxia, edema, central nervous system disorders, memory loss, or arterial disease. The present invention also provides methods for treating clinical conditions resulting from an abnormally high level of arginase activity, such as, heart disease, systemic hypertension, pulmonary hypertension, sexual dysfunction, autoimmune disease, chronic renal failure and cerebral vasospasm. The present invention also provides methods for treating clinical conditions associated with a deficient nitric oxide pathway by administering at least one N-hydroxyguanidine compound and, optionally, one or more vasoactive agents and/or thromboxane A2 receptor antagonists. The present invention also provides pharmaceutical compositions comprising at least one N-hydroxyguanidine compound, and, optionally, one or more vasoactive agents and/or thromboxane A2 receptor antagonists.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PRAI US 1998-87556P 19980601 (60) <--

SUMM Another embodiment of the invention provides methods of treating sexual dysfunctions in patients, including males and females, comprising administering to the patient a therapeutically effective amount of at least one N-hydroxyguanidine compound, such as N-hydroxy-L-arginine, and, optionally, at least one vasoactive agent and/or at least one thromboxane A2 receptor antagonist. Generally, the sexual dysfunction is attributable to low oxygen conditions. Preferably, the sexual dysfunctions are attributable to hypoxic ischemia, **neuropathy** or arterial disease.

DETD As used herein, "sexual dysfunction" includes any sexual dysfunction in a patient. The patient can be male or female. Sexual dysfunctions can include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunction refers to any female sexual dysfunction including, for example, sexual desire disorders, sexual arousal dysfunctions, orgasmic dysfunctions, sexual pain disorders, dyspareunia, and vaginismus. The female can be pre-menopausal or menopausal. Male sexual dysfunction refers to any male sexual dysfunction including, for example, male erectile dysfunction and impotence. In a preferred embodiment, "sexual dysfunctions" refer to sexual dysfunctions that are attributable to low oxygen conditions, including, but not limited to, sexual dysfunctions that are attributable to hypoxic ischemia, **neuropathy**, and arterial disease.

DETD A vasoactive agent is any therapeutic agent that can relax vascular and non-vascular smooth muscle. Suitable vasoactive agents include, but are not limited to, long and short acting .alpha.-adrenergic blockers (such as, for example, phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, yohimbine, moxisylyte); calcium channel blockers (such as, for example, nifedipine, veraparmil, diltiazem, gallopamil, niludipine, nimodipins, nicardipine); .beta.-blockers (such as, for example, butixamine, dichloroisoproterenol, propanolol, alprenolol, bunolol, nadolol, oxprenolol, perbutolol, pinodolol, sotalol, timolol, metoprolol, atenolol, acebutolol, bevantolol, pafenolol, tolamodol); phosphodiesterase inhibitors (such as, for example, papaverine, zaprinast, **sildenafil**); adenosine, ergot alkaloids (such as, for example, ergotamine, ergotamine analogs, including, for example, acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride, terguride); vasoactive intestinal peptides (such as, for example, peptide histidine isoleucine, peptide histidine methionine, substance P, calcitonin

gene-related peptide, neurokinin A, bradykinin, neurokinin B); dopamine agonists (such as, for example, apomorphine, bromocriptine, testosterone, cocaine, strychnine); opioid antagonists (such as, for example, naltrexone); prostaglandins (such as, for example, alprostadil, prostaglandin E.sub.2, prostaglandin F.sub.2, misoprostol, enprostil, arbaprostil, unoprostone, trimoprostil, carboprost, limaprost, gemeprost, lantanoprost, ornoprostil, beraprost, sulpostrone, rioprostil); endothelin antagonists (such as, for example, bosentan, sulfonamide endothelin antagonists, BQ-123, SQ 28608); potassium channel activators (such as, for example nicorandil, pinacidal, cromakalim) and mixtures thereof. Preferred are combinations of N-hydroxy-L-arginine with .alpha.-adrenergic antagonists, phosphodiesterase inhibitors, prostaglandins, dopamine agonists, potassium channel activators or endothelin antagonists.

L95 ANSWER 7 OF 17 USPATFULL
AN 2002:209529 USPATFULL
TI Combination effective for the treatment of impotence
IN Maytom, Murray C., Darien, CT, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6436944 B1 20020820
AI US 2000-636407 20000810 (9)
PRAI US 1999-156750P 19990930 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Rose, Shep K.
LREP Richardson, Peter C., Benson, Gregg C., Musser, Arlene K.
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 880
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the treatment of erectile dysfunction with a combination of (1) a compound selected from potassium channel openers, and (2) a compound selected from compounds which elevate cGMP levels. **Sildenafil** or a pharmaceutically acceptable salt thereof is preferred as the cGMP PDE elevator. Also included are compositions and kits comprising such impotence treating compounds.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-156750P 19990930 (60) <--
AB This invention relates to the treatment of erectile dysfunction with a combination of (1) a compound selected from potassium channel openers, and (2) a compound selected from compounds which elevate cGMP levels. **Sildenafil** or a pharmaceutically acceptable salt thereof is preferred as the cGMP PDE elevator. Also included are compositions and kits comprising such impotence treating compounds.
SUMM The penis normally becomes erect when certain tissues, in particular the corpora cavernosa in the central portion of the penis, become engorged with blood, thereby causing them to become less flaccid, and in turn causing an erection. Impotence can result from psychologic disturbances (psychogenic), from physiologic abnormalities (organic) or from a combination of both. Thus, in some males erectile dysfunction may be due to anxiety or depression, with no apparent somatic or organic impairment. In other cases, erectile dysfunction is associated with atherosclerosis of the arteries supplying blood to the penis. In still other cases, the dysfunction may be due to venous leakage or abnormal drainage in which there is leakage from veins in the penis such that sufficient pressure for an erection can be neither obtained nor maintained. In still other cases, the dysfunction is associated with a **neuropathy** or due to nerve damage arising from, for example, surgery or a pelvic injury. Typically, multiple factors are responsible for impotence.

SUMM Preferred cGMP PDE inhibitors include **sildenafil** which has the structure: ##STR1##

SUMM A preferred pharmaceutically acceptable salt of **sildenafil** for use in this invention is the **citrate** salt.

SUMM Preferred potassium channel openers include nicorandil, diazoxide, cromakalim, levcromakalim, pinacidil, lemakalim and minoxidil and also pharmaceutically acceptable salts or isomers thereof. Especially preferred potassium channel openers include nicorandil, diazoxide and minoxidil. Preferred specific combinations include any of these in combination with **sildenafil** or a pharmaceutically acceptable salt thereof, particularly the **citrate** salt. Most preferred are **sildenafil citrate** in combination with nicorandil. A variety of potassium channel openers are described in U.S. Pat. Nos. 5,464,867; 5,466,712; 5,403,853; 5,403,854; 5,397,790; 5,401,753; 5,872,139; and 5,905,156, the teachings of which are incorporated herein by reference.

SUMM Specific combinations of a potassium channel opener and a cGMP elevator useful in this invention include any potassium channel opener in combination with **sildenafil**. Combinations of **sildenafil**, especially **sildenafil citrate**, with a potassium channel opener, including any of those previously noted, are preferred.

CLM What is claimed is:
5. A method as defined in claim 4 wherein said cGMP PDE inhibitor is **sildenafil** or a pharmaceutically acceptable salt thereof.

10. A method as defined in claim 1 wherein said first compound is nicorandil or a pharmaceutically acceptable salt thereof and said second compound is **sildenafil** or a pharmaceutically acceptable salt thereof.

18. A method as defined in claim 17 wherein said cGMP PDE inhibitor is **sildenafil** or a pharmaceutically acceptable salt thereof.

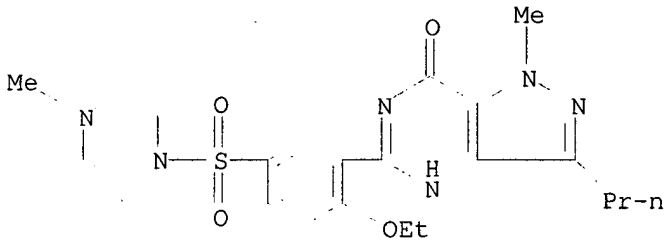
23. A method as defined in claim 14 which comprises (1) nicorandil; and (2) **sildenafil** or a pharmaceutically acceptable salt thereof.

IT 364-98-7, Diazoxide 38304-91-5, Minoxidil 60560-33-0, Pinacidil 65141-46-0, Nicorandil 94470-67-4, Cromakalim **139755-83-2**, Sildenafil **171599-83-0**, Sildenafil citrate 247580-96-7 247580-98-9 247581-02-8 247581-08-4 247581-65-3 247581-76-6 247581-77-7 247582-13-4 247582-31-6 247582-39-4 266352-92-5
(pharmaceuticals comprising potassium-channel-opener and cGMP PDE elevator for treatment of impotence)

IT **139755-83-2**, Sildenafil **171599-83-0**, Sildenafil citrate
(pharmaceuticals comprising potassium-channel-opener and cGMP PDE elevator for treatment of impotence)

RN 139755-83-2 USPATFULL

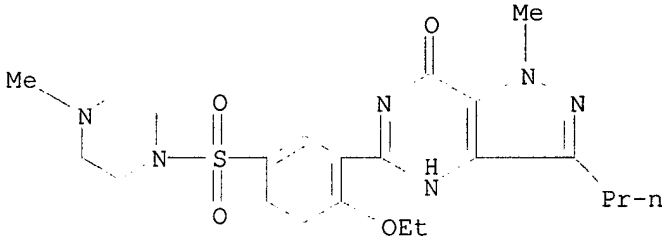
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



RN 171599-83-0 USPATFULL
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

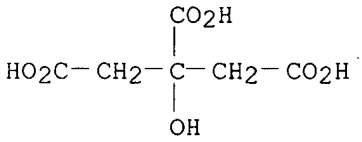
CM 1

CRN 139755-83-2
CMF C22 H30 N6 O4 S



CM 2

CRN 77-92-9
CMF C6 H8 O7



L95 ANSWER 8 OF 17 USPATFULL
AN 2002:129960 USPATFULL
TI Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors
IN Du Bois, Daisy Joe, Palo Alto, CA, United States
PA Pfizer Inc., New York, NY, United States (U.S. corporation)
PI US 6399601 B1 20020604
AI US 2000-670759 20000927 (9)
PRAI US 1999-157148P 19990930 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Ramsuer, Robert W.; Assistant Examiner: Wright, Sonya
LREP Richardson, Peter C., Benson, Gregg C., Crissey, Todd M.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1

DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 4218
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to compounds of Formula I ##STR1##

or stereoisomers, pharmaceutically acceptable salts or prodrugs thereof or a pharmaceutically acceptable salts of the prodrugs. This invention also relates to pharmaceutical compositions comprising a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-157148P 19990930 (60) <--
AB or stereoisomers, pharmaceutically acceptable salts or prodrugs thereof or a pharmaceutically acceptable salts of the prodrugs. This invention also relates to pharmaceutical compositions comprising a compound of Formula I, and to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.
SUMM This invention relates to bicyclic pyrrolyl amides and pharmaceutical compositions comprising bicyclic pyrrolyl amides. This invention also relates to the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, and tissue ischemia, particularly myocardial ischemia, using the bicyclic pyrrolyl amides.

SUMM Also provided are methods of treating diabetic **neuropathy**, the methods comprising the step of administering to a patient having diabetic **neuropathy** a therapeutically effective amount of a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs.

SUMM Also provided are kits for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts in a patient having diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts, the kits comprising:

SUMM b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, or cataracts; and

SUMM Also provided are kits for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia in a patient having diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the kits comprising:

SUMM b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy,

cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia; and

SUMM Also provided are methods of treating diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the method comprising the step of administering to a patient having diabetes, insulin resistance, diabetic **neuropathy** , diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, a therapeutically effective amount of a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs in combination with at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM Also provided are pharmaceutical compositions comprising a compound of Formula I, stereoisomers, pharmaceutically acceptable salts and prodrugs thereof, and pharmaceutically acceptable salts of the prodrugs and at least one additional compound useful to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM The present invention relates to compounds of Formula I, stereoisomers of compounds of Formula I, pharmaceutically acceptable salts of compounds of Formula I, prodrugs of compounds of Formula I, and pharmaceutically acceptable salts of the prodrugs of compounds of Formula I. The invention also relates to methods of treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, and tissue ischemia, particularly myocardial ischemia, and to pharmaceutically acceptable compositions comprising a compound of Formula I, stereoisomers of compounds of Formula I, pharmaceutically acceptable salts of compounds of Formula I, prodrugs of compounds of Formula I, and pharmaceutically acceptable salts of the prodrugs of compounds of Formula I.

SUMM A patient in need of glycogen phosphorylase inhibition is a patient having a disease or condition in which glycogen phosphorylase plays a role in the disease of condition. Examples of patients in need of glycogen phoshphorylase inhibition include patients having diabetes (including Type I and Type II, impaired glucose tolerance, insulin resistance, and the diabetic complications, such a nephropathy, retinopathy, **neuropathy** and cataracts), hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis and tissue ischemia.

SUMM In another aspect, the present invention concerns the treatment of diabetes, including impaired glucose tolerance, insulin resistance, insulin dependent diabetes mellitus (Type I) and non-insulin dependent diabetes mellitus (NIDDM or Type II). Also included in the treatment of diabetes are the treatment of the diabetic complications, such as **neuropathy**, nephropathy, retinopathy or cataracts.

SUMM Diabetes can be treated by administering to a patient having diabetes

(Type I or Type II), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as **neuropathy**, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a compound of the present invention. It is also contemplated that diabetes be treated by administering a compound of the present invention or an other glycogen phosphorylase inhibitor in combination with an additional agent that can be used to treat diabetes and/or obesity. Preferred gylcogen phosphorylase inhibitors that are useful in combination with other agents useful to treat diabetes and/or obesity include those of Formula I. Additional preferred gylcogen phosphorylase inhibitors are disclosed in PCT publications WO 96/39384 and WO 96/39385.

SUMM Representative agents that can be used to treat diabetes include insulin and insulin analogs: (e.g., LysPro insulin. inhaled formulations comprising insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)NH.sub.2; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; .alpha.2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, insulinotropin, exendin-4, BTS-67582, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; RXR agonists: JTT-501, MCC-555, MX-6054, DRF2593, GI-262570, KRP-297, LG100268; fatty acid oxidaton inhibitors: clomoxir, etomoxir; .alpha.-glurosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; .beta.-agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243, TAK-667, AZ40140; phosphodiesterase inhibitors, both cAMP and cGMP type: **sildenafil**, L686398: L-386,398; lipid-lowering agents: benfluorex, atorvastatin; antiobesity agents: fenfluramine, orlistat, sibutramine; vanadate and vanadium complexes (e.g., Naglivan.RTM.) and peroxovanadium complexes; amylin antagonists: pramlintide, AC-137; lipoxygenase inhibitors: masoprocal; somatostatin analogs: BM-23014, seglitide, octreotide; glucagon antagonists: BAY 276-9955; insulin signaling agonists, insulin mimetics, PTP1B inhibitors: L-783281, TER17411, TER17529; gluconeogenesis inhibitors:GP3034; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994; glucose transport stimulating agents: BM-130795; glucose synthase kinase inhibitors: lithium chloride, CT98014, CT98023; galanin receptor agonisnts; MTP inhibitors such as those disclosed in U.S. provisional patent application No. 60/164,803; growth hormone secretagogues such as those disclosed in PCT publication numbers WO 97/24369 and WO 98/58947; NPY antagonists: PD-160170, BW-383, BW1229, CGP-71683A, NGD 95-1, L-152804; Anorectic agents including 5-HT and 5-HT2C receptor antagonists and/or mimetics: dexfenfluramine, Prozac.RTM., Zoloft.RTM.; CCK receptor agonists: SR-27897B; galanin receptor antagonists; MCR-4 antagonists: HP-228; leptin or mimetics:leptin; 11-beta-hydroxysteroid dehydrogenase type-I inhibitors; urocortin mimetics, CRF antagonists, and CRF binding proteins: RU486, urocortin. Other anti-diabetic agents that can be used in combination with a glycogen phosphorylase inhibitor include ergoset and D-chiroinositol. Any combination of agents can be administered as described above.

SUMM In addition to the categories and compounds mentioned above, gylcogen phosphorylase inhibitors, preferrably the compounds of the present invention, can be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol dehydrogenase inhibitors, or combinations thereof, to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic

retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, particularly myocardial ischemia.

SUMM Each of the thyromimetic compounds referenced above and other thyromimetic compounds can be used in combination with the compounds of the present invention to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or issue ischemia.

SUMM The compounds of the present invention can also be used in combination with aldose reductase inhibitors. Aldose reductase inhibitors constitute a class of compounds that have become widely known for their utility in preventing and treating conditions arising from complications of diabetes, such as diabetic **neuropathy** and nephropathy. Such compounds are well known to those skilled in the art and are readily identified by standard biological tests. For example, the aldose reductase inhibitors zopolrestat, 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-, and related compounds are described in U.S. Pat. No. 4,939,140 to Larson et al.

SUMM Each of the aldose reductase inhibitors referenced above and other aldose reductase inhibitors can be used in combination with the compounds of the present invention to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM The compounds of the present invention can also be used in combination with sorbitol dehydrogenase inhibitors. Sorbitol dehydrogenase inhibitors lower fructose levels and have been used to treat or prevent diabetic complications such as **neuropathy**, retinopathy, nephropathy, cardiomyopathy, microangiopathy, and macroangiopathy. U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitof dehydrogenase.

SUMM Each of the sorbitol dehydrogenase inhibitors referenced above and other sorbitol dehydrogenase inhibitors can be used in combination with the compounds of the present invention to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

SUMM Each of the NHE-1 inhibitors referenced above and other NHE-1 inhibitors can be used in combination with the compounds of the present invention to treat or prevent diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

CLM What is claimed is:
7. A method of treating atherosclerosis, diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperglycemia, hypertension, tissue ischemia, or myocardial ischemia, the method comprising the step of administering to a patient having or at risk of having atherosclerosis, diabetes, Insulin

resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, hyperglycemia, hypertension, tissue ischemia, or myocardial ischemia a therapeutically effective amount of a compound of claim 1, a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug.

10. A kit for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or issue ischemia in a patient having diabetes, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the kit comprising: a) a first pharmaceutical composition comprising a compound in accordance with claim 1, or a stereoisomer, pharmaceutically acceptable salt or prodrug of the compound, or a pharmaceutically acceptable salt of the prodrug; b) a second pharmaceutical composition comprising a second compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia; and c) a container for containing the first and second compositions.

11. A method of treating diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, the method comprising the step of administering to a patient having diabetes, insulin its resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, a therapeutically effective amount of a compound of claim 1, a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of a prodrug in combination with at least one additional compound useful for the treatment of diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

12. A pharmaceutical composition comprising a compound of claim 1, a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug and at least one additional compound useful to treat diabetes, insulin resistance, diabetic **neuropathy**, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

IT **Nerve, disease**
(diabetic neuropathy, treatment; prepn. of bicyclic pyrrolylcarboxamides as glycogen phosphorylase inhibitors)

L95 ANSWER 9 OF 17 USPATFULL
AN 2002:126808 USPATFULL
TI Use of CLC3 chloride channel blockers to modulate vascular tone
IN Lamb, Fred S., Solon, IA, UNITED STATES
Schutte, Brian C., Iowa City, IA, UNITED STATES
Yang, Baoli, Cedar Rapids, IA, UNITED STATES
PI US 2002065325 A1 20020530
AI US 2001-930105 A1 20010815 (9)

RLI Continuation-in-part of Ser. No. US 2000-512926, filed on 25 Feb 2000, PENDING
PRAI US 1999-121727P 19990226 (60) <--
DT Utility
FS APPLICATION
LREP SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A., P.O. BOX 2938, MINNEAPOLIS, MN, 55402
CLMN Number of Claims: 43
ECL Exemplary Claim: 1
DRWN 18 Drawing Page(s)
LN.CNT 2662
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods for the modulation of vascular tone in a patient having compromised vascular tissue, which methods comprise the administration of a chloride channel blocking agent or a pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1999-121727P 19990226 (60) <--
SUMM [0003] Male sexual dysfunction, or impotence, may be manifested in various ways: loss of desire, inability to obtain or maintain an erection, premature ejaculation, absence of emission, inability to achieve orgasm. The organic causes of erectile impotence can be grouped into endocrine, drug, local, neurologic, and vascular causes. Vascular insufficiency causes impotence because blood flow into the vascular network of the penis is insufficient to obtain (or maintain) the erect state. Likewise, occlusion in smaller vessels supplying the penis can also lead to impotence. Together with **neuropathy**, vascular insufficiency contributes to the impotence in many men with diabetes mellitus.

SUMM [0005] Medical therapy with androgens offers little more than placebo benefit except in hypogonadal men. Surgical therapy may be useful in the treatment of decreased potency related to aortic obstruction; however, potency can be lost rather than improved after aortic operation if the autonomic nerve supply to the penis is damaged. A useful surgical technique for improvement of potency in refractory patients such as individuals with diabetic **neuropathy** is the implantation of a penile prosthesis, e.g., the insertion within the corpora of a small, blunt, SILASTIC.RTM. rod. The patient must be made aware that full erection is not produced and that the device only prevents buckling during intercourse. Furthermore, the complication rate is high in some patients. Alternatively, an inflatable prosthetic device has been devised for implantation on either side of the corpora. A connecting reservoir of material is placed in the perivesicular space and pumps are located in the scrotum. By means of these pumps the penis can be made to become nearly fully erect at the appropriate time and to relax after intercourse.

SUMM [0009] The physiologic mechanism of erection of the penis involves the local release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme cyclic guanosine monophosphate (cGMP) producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. **Sildenafil** (**VIAGRA**.RTM.)) is reported to be a selective inhibitor of cyclic-GMP-specific phosphodiesterase type 5 (PDE5), the predominant isozyme metabolizing cyclic GMP formed in the corpus cavernosum. Since **sildenafil** is a potent inhibitor of PDE5 in the corpus cavernosum, it is believed to enhance the effect of nitric oxide, thereby increasing cavernosal blood flow in the penis, especially with sexual stimulation. Inhibitors of cyclic guanosine 3', 5'-monophosphate phosphodiesterases (cGMP PDEs), such as **sildenafil**, are useful in the treatment of ED. As disclosed in PCT Publication WO 94/28902,

sildenafil compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. Inasmuch as **sildenafil** at the currently recommended doses of 25-100 mg has little effect in the absence of sexual stimulation, **sildenafil** is believed to restore the natural erectile response to sexual stimulation but not cause erections in the absence of such stimulation. See, for example, Goldstein et al., The New England Journal of Medicine, 338, 1397-1404 (1998). The localized mechanism by which cGMP stimulates relaxation of the smooth muscles has not been elucidated.

SUMM [0010] In dose-response studies, increasing doses of **sildenafil** (25 to 100 mg) reportedly increased the erectogenic efficacy of **sildenafil**. However, the time to onset of action of periorally administered drugs is long and highly variable, due to differences in absorption based on a wide variety of factors, from the size and age of the patient to the interval since, and size and composition of, the last meal consumed by the patient. However, the oral administration of **sildenafil** is also accompanied by dose-responsive undesirable side effects. At dosages higher than 50 milligrams, the incidence of such side effects as abnormal vision problems ranging from blue or green halo effects to blurring, dyspepsia, nasal congestion, blinding headaches, flushing redness, diarrhea, dizziness, rash, and urinary tract infection increases. Other more serious side effects have been reported, such as syncope (loss of consciousness), priapism (erection lasting 4 hours or more) and increased cardiac risk (coital coronaries), can be brought on in some cases by physiological predisposition, adverse drug interaction or potentiation, or by drug abuse.

SUMM [0011] In addition, consistent with its known effects on the NO/cGMP pathway, **sildenafil** has been shown to potentiate the hypotensive effects of nitrates. Hypotension crisis can result from the combination of **sildenafil citrate** and organic nitrates, causing, in some cases death, so its administration to patients who are concurrently using organic nitrates (such as nitroglycerin) in any form is contraindicated. Moreover, the long-term effects of large doses of **sildenafil** containing drugs is not known. See, for example, Handy B., Time, 50-57 (May 4, 1998).

DETD [0074] By "compromised vascular tissue" is meant vascular tissue that is mechanically compromised, e.g., by a medical procedure, such as balloon angioplasty, which results in damage or disruption to the endothelial cell monolayer associated with smooth muscle cells, or that is compromised by a disease-induced, genetically-influenced or other vascular disorder, such as diabetes, hypertension, vascular insufficiency or **neuropathy**, that either creates the risk or predisposition for damage to the endothelial cell monolayer associated with smooth muscle cells or results in an abnormal, i.e., unhealthy, vasculature.

DETD [0180] For **neuropathological** studies, wild type, heterozygous and knockout mice were sacrificed at a series of postnatal ages. These ages included postnatal day (PD) 24, PD75 (2.5 months), PD165 (5.5 months), PD270 (9 months) and PD330 (11 months). Three animals of each genotype were included at each time point. Following a lethal injection of pentobarbital (>50 mg/kg, i.p., to effect), the mice were perfused via the left ventricle with ice cold 0.9% saline, followed by a fixative containing 4% paraformaldehyde in 0.1 M phosphate buffer. The brains were removed and stored in cold fixative for a minimum of 1 week. Next, some of the brains were dehydrated through a graded series of alcohol, prior to paraffin embedment. The paraffin-embedded tissue was cut on a rotary microtome in the coronal plane at a thickness of 6 micrometers. Sections throughout the rostral-caudal axis of the brain were mounted onto glass slides and stained with cresyl violet. The remaining fixed

brains were placed into 30% sucrose in 0.1 M sodium phosphate until they sank. Forty-micrometer-thick frozen sections were cut horizontally on a sliding microtome. A 1:4 series of sections were mounted onto glass slides and were Nissl-stained with cresyl violet. All samples were examined by light microscopy.

IT **Nerve, disease**

IT **Nerve, disease**

(death; use of CLC3 chloride channel blockers to modulate vascular tone)

L95 ANSWER 10 OF 17 USPATFULL

AN 2002:26868 USPATFULL

TI Methods and transdermal compositions for pain relief

IN Murdock, Robert W., Selah, WA, UNITED STATES
Williams, C. Donald, Yakima, WA, UNITED STATES

PI US 2002015713 A1 20020207

AI US 2001-825524 A1 20010402 (9)

RLI Continuation-in-part of Ser. No. US 2001-754500, filed on 3 Jan 2001, PENDING Continuation-in-part of Ser. No. US 1999-342679, filed on 29 Jun 1999, ABANDONED Continuation-in-part of Ser. No. WO 1999-US14653, filed on 29 Jun 1999, UNKNOWN Continuation-in-part of Ser. No. US 1998-106684, filed on 29 Jun 1998, PENDING Continuation-in-part of Ser. No. WO 1997-US19651, filed on 24 Oct 1997, UNKNOWN Continuation-in-part of Ser. No. US 1997-957485, filed on 24 Oct 1997, ABANDONED

PRAI US 1999-122903P 19990305 (60) <--
US 1996-29120P 19961024 (60) <--

DT Utility

FS APPLICATION

LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109

CLMN Number of Claims: 19

ECL Exemplary Claim: 1

DRWN 11 Drawing Page(s)

LN.CNT 1987

AB The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

PRAI US 1999-122903P 19990305 (60) <--

PRAI US 1996-29120P 19961024 (60) <--

DETD [0025] As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and **neuropathic** pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

DETD [0062] In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as **sildenafil**, sold under the tradename **Viagra**. It is believed that transdermal administration of **sildenafil** may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

DETD [0126] 0.15 grams **sildenafil** was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant

composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

DETD [0127] A mixture of **Sildenafil** 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered **Sildenafil**, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

DETD [0169] Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., **neuropathic** pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

DETD [0170] Carbamazepine appears to provide positive effects as a pain, e.g., **neuropathic** pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

L95 ANSWER 11 OF 17 USPATFULL
AN 2002:16611 USPATFULL
TI Methods and transdermal compositions for pain relief
IN Murdock, Robert W., Selah, WA, UNITED STATES
Williams, C. Donald, Yakima, WA, UNITED STATES
PA Praecis Pharmaceuticals, Inc. (U.S. corporation)
PI US 2002009487 A1 20020124
US 6479074 B2 20021112
AI US 2001-825375 A1 20010402 (9)
RLI Division of Ser. No. US 1999-342679, filed on 29 Jun 1999, ABANDONED Division of Ser. No. US 1998-106684, filed on 29 Jun 1998, GRANTED, Pat. No. US 6290986 Continuation-in-part of Ser. No. US 1997-957485, filed on 24 Oct 1997, ABANDONED
PRAI WO 1997-US19651 19971024 <--
US 1999-122903P 19990305 (60) <--
US 1996-29120P 19961024 (60) <--
DT Utility
FS APPLICATION
LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
CLMN Number of Claims: 53
ECL Exemplary Claim: 1
DRWN 11 Drawing Page(s)
LN.CNT 2027
AB The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

PRAI WO 1997-US19651 19971024 <--
PRAI US 1999-122903P 19990305 (60) <--
PRAI US 1996-29120P 19961024 (60) <--
DETD [0021] As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel

syndrome; myofascial pain, and **neuropathic** pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

DETD [0063] In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as **sildenafil**, sold under the tradename **Viagra**. It is believed that transdermal administration of **sildenafil** may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

DETD [0129] 0.15 grams **sildenafil** was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

DETD [0130] A mixture of **Sildenafil** 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered **Sildenafil**, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

DETD [0180] Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., **neuropathic** pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

DETD [0181] Carbamazepine appears to provide positive effects as a pain, e.g., **neuropathic** pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

L95 ANSWER 12 OF 17 USPATFULL
AN 2002:13808 USPATFULL
TI Natural composition for the treatment of circulatory conditions
IN Duckett, Melvin J., 10300 Cedar Grave Rd., Sparks, MD, United States 21152
Moore, Kyle, 4705 Creekside Cir., Apt. 13, Owings Mills, MD, United States 21117
PI US 6340480 B1 20020122
AI US 1999-473105 19991228 (9)
RLI Continuation-in-part of Ser. No. US 1999-255587, filed on 22 Feb 1999, now patented, Pat. No. US 6007824
PRAI US 1998-92143P 19980709 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Tate, Christopher R.
LREP Law Office of Royal W. Craig
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 367
AB A composition and method for treating circulatory conditions by promoting systemic vascular relaxation and dilation. Exemplary

circulatory conditions are disclosed and include wound healing and/or reduction of hypertension. The composition is a natural combination of L-arginine, ginseng and Zizyphi fructus in an orally or topically administered dosage. The combination works synergistically to synthesize NO and thereby promote systemic vascular relaxation and dilation. The mechanism works in the wound compartment to promote and sustain the wound healing process. Likewise, the combined constituents, when administered orally or topically in proper concentration, work to maintain a critical threshold level of NO in areas that cannot themselves produce it, thereby promoting systemic vascular relaxation and dilation in order to reduce hypertension.

PRAI US 1998-92143P 19980709 (60) <--

SUMM One example of such a condition plus a useful treatment compound is set forth in co-pending U.S. utility patent application No. 09/255,587 (now issued as U.S. Pat. No. 6,007,824 to the inventors named herein). A composition and method for treating sexual dysfunction was therein disclosed, the natural composition including a combination of L-arginine, ginseng and Zizyphi fructus in an orally administered dosage. The combination acts synergistically to alleviate erectile dysfunction by stimulating enough release of NO in the corpus cavernosum to produce and sustain smooth muscle relaxation, thereby allowing the inflow of blood and alleviating erectile dysfunction. The '587 patent effectively provides a natural medicinal alternative to **Viagra** .RTM. for the treatment of erectile dysfunction.

SUMM Nitric oxide regulation of wound repair invokes the following relationships: wound oxygen availability is enhanced by the vasodilator functions of nitric oxide (this is a key factor in the endothelial-mediated microvascular homeostasis that is exhibited in cutaneous tissue); nitric oxide has been demonstrated to be a significant component of the neurogenic vascular response; local random flap survival is dependent upon sustained nitric oxide activity and nitric oxide deficiency has been clinically and experimentally associated with the **neuropathic** (ischemic) alterations observed in diabetes; the inflammatory mediation of wound repair is enhanced by nitric oxide mediated antimicrobial cytotoxicity and immunomodulation; wound angiogenesis is enhanced through nitric oxide mediated mechanisms; intravascular cellular adhesion (neutrophilendothelial) is inhibited by the action of nitric oxide on the integrins pathway; nitric oxide activity also decreases extravascular free radical cellular peroxidation by integrins inhibition. In addition, wound matrix development and remodeling are enhanced by the increased collagen deposition and wound tensile strength mediated by nitric oxide. Fibroblast chemotaxis and migration are enhanced by nitric oxide activity, endothelial and epithelial cell proliferation and apoptosis regulation may also be correlated to wound nitric oxide activity. Boykin, J. V., Nitric Oxide in Wound Healing. See, also, Bauer J. A., Hvdroxocobalamins as Biologically Compatible Donors of Nitric Oxide Implicated in the Acceleration of Wound Healing, Med Hypotheses, Jul. 1998 51:1, 65-7.

L95 ANSWER 13 OF 17 USPATFULL
AN 2001:176599 USPATFULL
TI Methods and transdermal compositions for pain relief
IN Murdock, Robert W., Selah, WA, United States
Williams, C. Donald, Yakima, WA, United States
PI US 2001029257 A1 20011011
AI US 2001-754500 A1 20010103 (9)
RLI Continuation-in-part of Ser. No. US 1999-342679, filed on 29 Jun 1999, ABANDONED Continuation-in-part of Ser. No. US 1998-106684, filed on 29 Jun 1998, PENDING Continuation-in-part of Ser. No. US 1997-957485, filed

on 24 Oct 1997, ABANDONED
PRAI WO 1997-US19651 19971024 <--
WO 1999-US14653 19990629 <--
US 1999-122903P 19990305 (60) <--
US 1996-29120P 19961024 (60) <--
DT Utility
FS APPLICATION
LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
CLMN Number of Claims: 57
ECL Exemplary Claim: 1
DRWN 11 Drawing Page(s)
LN.CNT 2093
AB The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

PRAI WO 1997-US19651 19971024 <--
PRAI WO 1999-US14653 19990629 <--
PRAI US 1999-122903P 19990305 (60) <--
PRAI US 1996-29120P 19961024 (60) <--
DETD [0022] As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and **neuropathic** pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.
DETD [0065] In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as **sildenafil**, sold under the tradename **Viagra**. It is believed that transdermal administration of **sildenafil** may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.
DETD [0133] 0.15 grams **sildenafil** was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.
DETD [0134] A mixture of **Sildenafil** 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered **Sildenafil**, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.
DETD [0194] Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., **neuropathic** pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other

pharmaceuticals as described herein.
DETD [0195] Carbamazepine appears to provide positive effects as a pain, e.g., **neuropathic** pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

L95 ANSWER 14 OF 17 USPATFULL
AN 2001:157822 USPATFULL
TI Method and composition for transdermal administration of pharmacologic agents
IN Murdock, Robert W., Selah, WA, United States
Williams, C. Donald, Yakima, WA, United States
PA Pharmaceutical Applications Associates, LLC, Yakima, WA, United States (U.S. corporation)
PI US 6290986 B1 20010918
AI US 1998-106684 19980629 (9)
RLI Continuation-in-part of Ser. No. WO 1997-US19651, filed on 24 Oct 1997
Continuation-in-part of Ser. No. US 1997-957485, filed on 24 Oct 1997, now abandoned
PRAI US 1996-29120P 19961024 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala, Lakshmi
LREP Lahive & Cockfield, LLP, DeConti, Jr., Gjulio A., Laccotripe, Maria C.
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1431
AB A method and composition for transdermal delivery of pharmaceuticals or combinations of pharmaceuticals is provided. The pharmaceuticals are delivered using a matrix of a lecithin gel such as a lecithin organogel. A number of psychopharmaceuticals can be used including fluoxetine, sertraline, carbamazepine, paroxetine, amitriptyline, trazadone, venlafaxine, propranolol, buproprion, valproic acid, nefazodone, ketoprofen, gabapentin, piroxican, doxepin, guaifenesin, pemoline and doxepin and combinations.

PRAI US 1996-29120P 19961024 (60) <--
SUMM The present invention is directed to transdermal administration of pharmacologic agents, and in particular to transdermal administration of drugs including antidepressant serotonin specific reuptake inhibitors (as SSRIs) such as fluoxetine, antidepressants such as buproprion and reboxetine, tricyclic antidepressant medications that have **neuropathic** pain treatment efficacy such as amitriptyline and doxepin, mood stabilizers such as carbamazepine, or valproic acid, Attention Deficit Hyperactivity Disorder (ADHD) medications such as pemoline anti-inflammatory or analgesic medications such as ketoprofen or piroxicam, treatments for impotence such as **sildenafil** and or anti-convulsants believed to possess **neuropathic** pain treatment efficacy such as gabapentin, carbamazepine, or combinations thereof such as using a gel matrix, preferably a lecithin organogel and/or a polymer gel.

DETD Another type of psychopharmaceutical agent are those used for treating depression and/or **neuropathic** pain, two examples of which are generically available amitriptyline, sold under the trade name Elavil and doxepin sold under the tradename Sinequan. Oral administration of amitriptyline and doxepin may be sub-optimal when high local tissue concentrations are desired. Accordingly, transdermal delivery of amitriptyline and doxepin, according to embodiments of the present invention, is particularly useful.
DETD In some situations, a transdermal composition containing a combination

of doxepin or amitriptyline with carbamazepine or gabapentin is useful for treating **neuropathic** pain. It is believed that transdermal administration of such combination can be advantageous, for at least some patients, as compared to oral administration, because higher local drug concentrations at the sites(s) e.g. of injury can be achieved yielding an improved therapeutic response without systemic side effects such as weight gain, drowsiness, gastrointestinal upset and anticholinergic side effects (which include but are not limited to urinary retention, blurred vision and dry mouth).

DETD Another class of pharmaceutical that may be particularly useful for localizing the dosage via transdermal applications are anticonvulsant agents such as generically available carbamazepine and patent protected gabapentin (sold respectively under the trade names Tegretol and Neurontin). Gabapentin is an anticonvulsant agent that is believed to relieve pain by blocking GABA-B neuroreceptor pain sites. Both gabapentin and carbamazepine often relieve muscle spasms, and therefore alleviate chronic pain through that mechanism as well. In oral form, gabapentin has been described as useful for chronic pain and reflex sympathetic dystrophy. It has been found to be useful for alleviating the **neuropathic** component of pain resulting form cervical, thoracic, and lumbar spinal disk injury. Transdermal application of gabapentin and carbamazepine are particularly effective means of obtaining higher local tissue concentrations of the medications, avoiding many systemic side effects, which can include fatigue, lethargy, and dizziness. The combinations described in some of the examples below are means of adding to the antispasmodic and analgesic properties of the gabapentin and carbamazepine.

DETD Another type of pharmaceutical that may be useful for transdermal application are those used for their analgesic and anti-inflammatory properties, or pain relief, such as ketoprofen and other non-steroidal anti-inflammatory drugs. For some patients, combinations of ketoprofen, doxepin, guaifenesin and/or carbamazepine have been demonstrated to be useful, e.g., for the treatment of superficial inflammation and swelling in combination with **neuropathic** pain, for example, in carpal tunnel syndrome, cervical disk and lumbar disk degenerative disease, occipital neuralgia, knee injuries including cartilage tears and joint surface damage, and similar degenerative processes involving the ankle and elbow. It has been demonstrated that administration of a combination of ketoprofen with other agents, particularly doxepin, gabapentin, and guaifenesin, can, for a majority of patients be useful as compared to oral agents, because it is believed that a composition combining ketoprofen with these agents provides substantially synergistic results, i.e. such that results are greater than the sum of results form ketoprofen alone in a transdermal application plus results from such additional components. It appears that the synergistic effect is most apparent when actual superficial swelling and inflammation is present; otherwise, use of the doxepin in combination with an anticonvulsant such as carbamazepine or gabapentin produces results that are not enhanced by the addition of ketoprofen. In some cases, guaifenesin has yielded a significant improvement in reduction of spasms, superior to that achieved with either carbamazepine or gabapentin. Guaifenesin is a centrally acting muscle relaxant. It is soluble in water, 1 gm at 25 degrees, and soluble in some organic solvents. Thus it appears to be on the border of oil and water solubility. Without wishing to be be bound by any theory, it is believed this attribute may help explain, at least in part, the utility of guaifenesin (and, for similar reasons, fluoxetine) as a transdermal agent.

DETD Another type of pharmaceutical that may be useful for transdermal administration includes pharmaceuticals used in treatment of impotence such as **sildenafil**, sold under the tradename **Viagra**.
It is believed that transdermal administration of **sildenafil** may be useful, for at least some patients, as compared to oral administration which has been found, in at least some situations, to be

associated with gastrointestinal side effects. Reports of deaths of **sildenafil** users may be an additional reason to consider a transdermal application method.

DETD Detailed examples of the preparation are provided below, along with examples of results obtained or expected from transdermal administration to human patients. Typically, the gel preparation was or will be applied to either volar surface of the lower arm of the patient, the post-auricular (behind the ear) region, or at the painful site when treating **neuropathic** pain. Laboratory measures of plasma blood levels were or will be obtained as shown in the examples below. The results generally demonstrate or are expected to demonstrate good absorption transdermally using lecithin organogel matrix as the vehicle. In circumstances where the objective was to treat **neuropathic** or chronic pain, only local effects were required and plasma blood levels were not obtained. Some patients were or will be evaluated by means of a structured evaluation form (FIG. 1), completed at a frequency of at least one time per week. Patients were or will be evaluated both for all the present symptoms as well as any side effects from currently administered medications. This is believed to make it possible to note changes on an ongoing basis. In general, for psychiatric patients, those with the most clear cut and uncomplicated diagnoses of major depression experienced, or are expected to experience, the best results. Patients with severe personality disorders or with concealed substance abuse disorders generally did less well.

DETD 0.15 grams **sildenafil** was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

DETD A mixture of **Sildenafil** 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered **Sildenafil**, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

DETD Based at least partially on the results described herein, a number of conclusions can be drawn. It appears doxepin is an effective **neuropathic** pain medication when administered transdermally and appears to be substantially free of side effects when administered by means of the gel utilized as a transport vehicle as described herein. Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a **neuropathic** pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein. Carbamazepine appears to provide positive effects as a **neuropathic** pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation. These side effects appear similar to those that are noted for oral administration of carbamazepine. Gabapentin appears to be free of side effects when administered transdermally. Although some patients appear to derive some benefit from a combination of transdermally administered ketoprofen, gabapentin, and prioxicam, the effect appears to be relatively weak compared to the effect provided by doxepin. Guaifenesini appears to provide benefit at least as an adjunctive treatment, of painful spasticity. There are some

difficulties in combining guaifenesin with doxepin in gel to yield a stable non-separating mixture. In many situations it appeared that a patient who applied an analgesic gel to more than one site described different degrees of pain relief for different body parts. For the patient population described herein, amitriptyline appeared to offer only limited pain relief when administered transdermally. It appears that combining gabapentin with doxepin may offer some additional benefit. The addition of guaifenesin to doxepin may be of particular value when painful spasticity is present.

DETD In light of the above description, a number of advantages of the present invention can be seen. The present invention provides for psychopharmaceutical and other pharmaceutical treatment using a transdermal delivery system. The invention makes it possible to provide such treatment to patients for whom oral delivery is suboptimal, such as patients who experience gastrointestinal or other side effects, patients who experience poor absorption for orally delivered pharmaceuticals and/or patients who benefit from delivery over an extended period or a relatively rapid delivery or higher rate of increase of plasma levels. The present invention is able to achieve delivery of therapeutic amounts of pharmaceuticals, for at least some patient populations, substantially without skin irritation, gastrointestinal or other side effects associated with orally-delivered pharmaceuticals, especially psychopharmaceuticals, and yields clinical benefits comparable to or greater than those received by patients to whom corresponding pharmaceuticals were administered orally. Although numerous examples of compostions which appear to be useful are disclosed herein, it is currently believed that among the most effective **neuropathic** pain medications are those described in examples 65, 67, 69 and 70.

L95 ANSWER 15 OF 17 USPATFULL
AN 2001:136687 USPATFULL
TI Treatment of sexual dysfunction with N-hydroxyguanidine compounds
IN de Tejada, Inigo Saenz, Madrid, Spain
PA NitroMed, Inc., Bedford, MA, United States (U.S. corporation)
PI US 6277884 B1 20010821
AI US 1999-321584 19990528 (9)
PRAI US 1998-87556P 19980601 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Hale and Dorr LLP
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 21 Drawing Page(s)
LN.CNT 1241
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods of treating sexual dysfunctions in patients by administering at least one N-hydroxyguanidine compound that is a substrate for nitric oxide synthase, and, optionally, one or more vasoactive agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1998-87556P 19980601 (60) <--
SUMM Another embodiment of the invention provides methods of treating sexual dysfunctions in patients, including males and females, comprising administering to the patient a therapeutically effective amount of at least one N-hydroxyguanidine compound, such as N-hydroxy-L-arginine, and, optionally, at least one vasoactive agent. Generally, the sexual dysfunctions are attributable to low oxygen conditions. Preferably, the sexual dysfunctions are attributable to hypoxic ischemia, **neuropathy** or arterial disease.

DETD As used herein, "sexual dysfunction" includes any sexual dysfunction in

a patient. The patient can be male or female. Patient refers to animals, preferably mammals, more preferably humans. Sexual dysfunctions can include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunction refers to any female sexual dysfunction including, for example, sexual desire disorders, sexual arousal dysfunctions, orgasmic dysfunctions, sexual pain disorders, dyspareunia, and vaginismus. The female can be pre-menopausal or menopausal. Male sexual dysfunction refers to any male sexual dysfunction including, for example, male erectile dysfunction and impotence. In a preferred embodiment, "sexual dysfunctions" refer to sexual dysfunctions that are attributable to low oxygen conditions, including, but not limited to, sexual dysfunctions that are attributable to hypoxic ischemia, **neuropathy**, and arterial disease.

DETD N-hydroxyguanidine compounds that are substrates for nitric oxide synthase can be administered with other compounds, such as vasoactive agents. A vasoactive agent is any therapeutic agent that can relax vascular and non-vascular smooth muscle. Suitable vasoactive agents include, but are not limited to, long and short acting .alpha.-adrenergic blockers (such as, for example, phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, yohimbine, moxisylyte); calcium blockers (such as, for example, nifedipine, veraparmil, diltiazem, gallopamil, niludipine, nimodipins, nicardipine); .beta.-blockers (such as, for example, butixamine, dichloroisoproterenol, propanolol, alprenolol, bunolol, nadolol, oxprenolol, perbutolol, pinodolol, sotalol, timolol, metoprolol, atenolol, acebutolol, bevantolol, pafenolol, tolamodol); phosphodiesterase inhibitors (such as, for example, papaverine, zaprinast, **sildenafil**); adenosine, ergot alkaloids (such as, for example, ergotamine, ergotamine analogs, including, for example, acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride, terguride); vasoactive intestinal peptides (such as, for example, peptide histidine isoleucine, peptide histidine methionine, substance P, calcitonin gene-related peptide, neurokinin A, bradykinin, neurokinin B); dopamine agonists (such as, for example, apomorphine, bromocriptine, testosterone, cocaine, strychnine); opioid antagonists (such as, for example, naltrexone); prostaglandins (such as, for example, alprostadil, prostaglandin E.sub.2, prostaglandin F.sub.2, misoprostol, enprostil, arbaprostil, unoprostone, trimoprostil, carboprost, limaprost, gemeprost, lantanoprost, ornoprostil, beraprost, sulpostrone, rioprostil); endothelin antagonists (such as, for example, bosentan, sulfonamide endothelin antagonists, BQ-123, SQ 28608); potassium channel activators (such as, for example nicorandil, pinacidal, cromakalim) and mixtures thereof. Preferred are combinations of N-hydroxy-L-arginine with .alpha.-adrenergic antagonists, phosphodiesterase inhibitors, prostaglandins, dopamine agonists, potassium channel activators or endothelin antagonists.

CLM What is claimed is:
10. The method of claim 1, wherein the sexual dysfunction is attributable to **neuropathy**.

L95 ANSWER 16 OF 17 USPATFULL
AN 2001:36442 USPATFULL
TI Method of administration of **sildenafil** to produce instantaneous response for the treatment of erectile dysfunction
IN Hussain, Anwar A., 886 McMeekin Pl., Lexington, KY, United States 40502
Dittert, Lewis W., 4999 Hartland Pkwy., Lexington, KY, United States 40515
PI US 6200591 B1 20010313
AI US 1998-208439 19981210 (9)

PRAI US 1998-90740P 19980625 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Azpuru, Carlos A.
LREP Burns, Doane, Swecker & Mathis, L.L.P.
CLMN Number of Claims: 12
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 641
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a method of rapidly and reliably delivering **sildenafil**, or derivatives thereof, alone or in combination with other compounds, to the systemic circulation by administration via the nasal route so as to produce virtually instantaneous onset of beneficial effects in the treatment of erectile dysfunction. The present invention further provides pharmaceutical compositions comprising **sildenafil**, or derivatives thereof, and/or pharmaceutically acceptable salts thereof in a variety of unique pharmaceutical dosage forms, with and without apomorphine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Method of administration of **sildenafil** to produce instantaneous response for the treatment of erectile dysfunction
PRAI US 1998-90740P 19980625 (60) <--
AB This invention provides a method of rapidly and reliably delivering **sildenafil**, or derivatives thereof, alone or in combination with other compounds, to the systemic circulation by administration via the nasal route so as to produce virtually instantaneous onset of beneficial effects in the treatment of erectile dysfunction. The present invention further provides pharmaceutical compositions comprising **sildenafil**, or derivatives thereof, and/or pharmaceutically acceptable salts thereof in a variety of unique pharmaceutical dosage forms, with and without apomorphine.
SUMM This invention relates to a method for greatly accelerating the rate of delivery of **sildenafil**, and derivatives thereof, to the central nervous system by administration via the nasal route to provide extremely rapid response in the treatment of erectile dysfunction in a patient in need of such prevention or treatment. This method provides response in less than five minutes, compared with 60 minutes or more required by the currently used oral route of administration.

SUMM Male sexual dysfunction, or impotence, may be manifested in various ways: loss of desire, inability to obtain or maintain an erection, premature ejaculation, absence of emission, inability to achieve orgasm. The organic causes of erectile impotence can be grouped into endocrine, drug, local, neurologic, and vascular causes. Vascular insufficiency causes impotence because blood flow into the vascular network of the penis is insufficient to obtain (or maintain) the erect state. Likewise, occlusion in smaller vessels supplying the penis can also lead to impotence. Together with **neuropathy**, vascular insufficiency contributes to the impotence in many men with diabetes mellitus.

SUMM Medical therapy with androgens offers little more than placebo benefit except in hypogonadal men. Surgical therapy may be useful in the treatment of decreased potency related to aortic obstruction; however, potency can be lost rather than improved after aortic operation if the autonomic nerve supply to the penis is damaged. A useful surgical technique for improvement of potency in refractory patients such as individuals with diabetic **neuropathy** is the implantation of a penile prosthesis, e.g., the insertion within the corpora of a small, blunt, Silastic.RTM. rod. The patient must be made aware that full erection is not produced and that the device only prevents buckling during intercourse. Furthermore, the complication rate is high in some

patients. Alternatively, an inflatable prosthetic device has been devised for implantation on either side of the corpora. A connecting reservoir of material is placed in the perivesicular space and pumps are located in the scrotum. By means of these pumps the penis can be made to become nearly fully erect at the appropriate time and to relax after intercourse.

SUMM It has recently been discovered that inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs) such as **sildenafil** are useful in the treatment of erectile dysfunction. As disclosed in PCT Publication WO 94/28902, the disclosure of which is hereby incorporated by reference, these compounds may be administered orally, thereby obviating the disadvantages associated with i.c. administration. However, the time to onset of action of periorally administered drugs is long and highly variable, due to differences in absorption based on a wide variety of factors, from the size and age of the patient to the interval since, and size and composition of, the last meal consumed by the patient. Currently, **sildenafil** must be administered orally about one hour prior to intercourse. This is a major drawback in situations where a rapid, reliable onset of effect is highly desirable for treatment to be considered optimal. Also, the long delay may lead to overdoses if the patient becomes impatient and decides to consume additional tablets in order to produce the desired effect.

SUMM Accordingly, a major object of the present invention is to provide a method for safely and conveniently administering **sildenafil** to a patient in need of treatment for erectile dysfunction in order to produce a reliable response in less than five minutes. The method comprises the intranasal administration of an effective amount of **sildenafil** to rapidly produce an erection sufficient to allow intercourse.

SUMM The objective of the present inventors is to improve the rate of delivery of **sildenafil** to the systemic circulation by administering **sildenafil** via the nasal route in order to speed the onset of effect and reduce the dose required for its beneficial effect. According to the method of the present invention, **sildenafil**, or derivatives thereof, may successfully be administered five to ten minutes prior to intercourse.

SUMM Practice of the method of the present invention will also result in lower plasma concentrations of metabolites of **sildenafil**, and derivatives thereof, and therefore fewer side effects. Intranasal delivery will improve drug bioavailability by direct absorption into the systemic circulation, thereby avoiding extensive hepatic and/or gut wall first-pass metabolism which may significantly lower the plasma concentrations of **sildenafil** when it is administered orally. As a result, small doses of **sildenafil**, or derivatives thereof, can be administered which will result in fewer side effects, and the drug will be more tolerable and more effective in patients suffering from erectile impotence. Most importantly, since **sildenafil** is effective immediately following intranasal administration, the patient is able to titrate himself until he achieves the desired response, rather than overdosing himself by swallowing an excessive number of tablets.

SUMM Intranasal dosage forms containing **sildenafil** in combination with other drugs used in the treatment of erectile dysfunction may also be employed in the practice of this method. Such additional drugs include, but are not limited to, apomorphine, papaverine, phentolamine, and phenoxybenzamine.

DRWD FIG. 1 represents a comparison of blood levels of **sildenafil**

following intravenous administration to those following intranasal administration.

DETD Thus, the present inventors have discovered a novel method for the delivery of **sildenafil**, or derivatives thereof, to a patient in need of such treatment, comprising the intranasal administration of **sildenafil**, or derivatives thereof. This method offers significant clinical advantages over the prior art. More specifically, the inventors sought to provide a rapid, reliable, safe, effective and convenient treatment for administering **sildenafil**, or derivatives thereof, to a patient in need of such treatment, which comprises the administration of **sildenafil**, or derivatives thereof, intranasally, thus providing nearly instantaneous response while avoiding the side-effects associated with oral dosage forms. Specifically, smaller doses of **sildenafil**, or derivatives thereof, can be administered through the nasal route, thus resulting in fewer side effects. By using the method of the present invention, which produces an instantaneous response, the drug will become more tolerable and more effective in treating patients suffering from erectile impotence.

DETD More particularly, the present invention concerns the intranasal administration of **sildenafil**, or derivatives thereof, having the chemical structure of formula (I): ##STR1##

DETD 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (**sildenafil**);

DETD The present inventors have found that intranasal administration of **sildenafil**, or derivatives thereof, effectively results in complete and very rapid absorption of these compounds into plasma. Intranasal administration of **sildenafil**, or derivatives thereof, is as effective as intravenous administration, but may be conveniently and painlessly self-administered by the patient. Intranasal administration can be employed at lower doses than oral administration, thereby allowing a decreased incidence of side effects.

DETD According to the present invention, **sildenafil**, or derivatives thereof, may be administered either as a free base, or in the form of a pharmaceutically acceptable salt thereof. Pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic center are, for example, non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acid, with organo-carboxylic acids, or with organo-sulphonic acids. Compounds of the formula (I) can also provide pharmaceutically acceptable metal salts, in particular non-toxic alkali metal salts, with bases. Examples include sodium and potassium salts.

DETD A still further aspect of this invention is a pharmaceutical composition of matter that comprises **sildenafil**, or derivatives thereof, as described above, and/or pharmaceutically acceptable salts thereof, and pharmaceutically acceptable carriers therefor.

DETD For therapeutic use in the treatment of erectile impotence, **sildenafil**, or derivatives thereof, or its salt, can be conveniently administered in the form of a pharmaceutical composition containing **sildenafil**, or derivatives thereof, or its salt, and a pharmaceutically acceptable carrier therefor. Typically, the carrier may be a liquid, solution, suspension, gel, or combinations thereof. In a preferred embodiment, the carrier is a pharmaceutically acceptable aqueous solution. Such compositions may require the use of one or more solubilizing agents to both effect dissolution of the drug(s) and/or keep them in aqueous solution. Such solubilizing agents include, but are not limited to nicotinamide, sodium saccharin, propylene glycol, glycerin, ethyl alcohol, etc. Suitable applications of solubilizing agents are exemplified below. Compositions according to the present invention may be prepared in accordance with accepted pharmaceutical procedures, for example, as described in Remington's Pharmaceutical Sciences, seventeenth edition, ed. Alfonso R. Gennaro,

Mack Publishing Company, Easton, Pa., Eighteenth edition (1990), which is hereby incorporated by reference.

DETD In addition to **sildenafil** and the ingredients particularly mentioned above, the formulations of this invention may also include other drugs used in the treatment of erectile dysfunction. Such additional drugs include, but are not limited to, apomorphine, papaverine, phentolamine, and phenoxybenzamine.

DETD According to the present invention, the term "patient" will encompass any mammal requiring treatment with **sildenafil**, or derivatives thereof, particularly a male human patient suffering from erectile impotence. In addition to the medical treatment of humans, this invention will also be applicable to the breeding of animals, such as horses and dogs, where artificial insemination may be prohibited.

DETD The dosage of **sildenafil**, or derivatives thereof, or pharmaceutically acceptable salts thereof in the compositions of the invention will vary depending on several factors, including, but not limited to, the age, weight, and species of the patient, the general health of the patient, the severity of the symptoms, whether the composition is being administered alone or in combination with other agents, the incidence of side effects and the like. The desired dose may be administered as needed, and may be administered repeatedly over a period of months or years. Higher and lower doses may also be administered. A major advantage of the present invention is the extremely rapid onset of response, which enables the patient to adjust the dose to produce only the desired effects and nothing more, thereby optimizing drug use and minimizing side-effects.

DETD The daily dose may be adjusted taking into account, for example, the above-identified variety of parameters. Typically, **sildenafil**, or derivatives thereof, may be administered in an amount of up to about 400 mg/day. Preferably, the amount of **sildenafil**, or derivatives thereof, administered will not exceed 300 mg/day. However, other amounts may also be administered, in particular, much smaller amounts of **sildenafil**, or derivatives thereof, will be required when administered intranasally, in accordance with the present invention.

DETD To achieve good plasma concentrations, the **sildenafil**, or derivatives thereof, may be administered, for instance, by intranasal administration of an approximate 0.1 to 1M solution of the active ingredient, optionally in saline.

DETD ABSORPTION OF SOLUBILIZED **SILDENAFIL** FROM THE NASAL CAVITY OF RATS

DETD These experiments determine the bioavailability of **sildenafil**, or derivatives thereof, after nasal administration and compare it to that after intravenous administration. In particular, the present experiment determined the absorption of **sildenafil** into the blood of rats following intranasal administration of a formulation in which the **sildenafil** was solubilized by the addition of mesylic acid (see below).

DETD The nasal absorption of **sildenafil**, or derivatives thereof, were measured using an in vivo technique in rats. Rats were fasted overnight prior to experimentation. Surgical procedures were performed under equithesin anesthesia (3 ml/kg, i.p.). An incision was made in the neck of each rat, and the trachea cannulated with polyethylene tubing (PF-260). A closed end tube was inserted through the esophagus to the posterior part of the nasal cavity to prevent drug from entering the esophagus. The nasopalatine passage was closed with an adhesive agent to prevent drainage of the drug from the nasal cavity to the mouth.

DETD Solutions of **sildenafil** hydrochloride (2 and 4 mg/rat/50 .mu.l) were prepared in water and administered through the right nostril using a microsyringe. For intravenous administration, the same dose of the drug was injected into the jugular vein (1 ml/kg body weight). Blood samples after nasal or intravenous drug administration were collected before and at 2, 15, 30, 60 and 120 min after drug administration,

centrifuged, and serum removed and stored (-80.degree. C.) until analysis.

DETD The main problem with preparing an intranasal dosage form of **sildenafil** is the limited solubility (3.5 mg/ml) of the **citrate** salt in water. This was overcome by solubilizing the **sildenafil citrate** with mesylic acid.

DETD **Sildenafil Citrate** 10 mg

DETD Assay Method for **Sildenafil** in Rat Blood

DETD At various times following the intranasal and intravenous administration of **sildenafil** to rats, the concentrations of **sildenafil** in blood were determined using the following analytical method:

DETD One hundred microliters of rat plasma was treated with 25 microliters of 1M monochloroacetic acid to denature the plasma proteins and release free **sildenafil**. Seventy-five microliters of acetonitrile was then added to precipitate the proteins. This solution was centifuged for 5 minutes at 5,000 g. The clear supernatant was injected onto the HPLC column.

DETD The mean concentrations (+/- standard deviations) of **sildenafil** found in the blood of rats at various times following the intranasal (n=5) and intravenous administrations (n=3) of the **sildenafil** solution described above are shown in Table 1. The concentrations are expressed as areas under the HPLC curves.times.10.sup.-4.

DETD Comparing the areas under the blood concentration versus time curves (see FIG. 1) shows that **sildenafil** is rapidly and complete absorbed following intranasal administration, and the peak blood concentration occurs at approximately 10 to 15 minutes following intranasal administration. These results indicate that the intranasal route produces much more rapid response in humans than does the current oral tablet formulation for which peak plasma concentrations are not achieved until 60 to 120 minutes following administration.

DETD TABLE 1

Concentration* of **Sildenafil** In the Blood of Rats

Time (min)	Intravenous Administration Mean (n = 3)	Standard Deviation	Intranasal Administration Mean (n = 5)	Standard Deviation
0	188.8	21.0	11.7	1.3
2	84.7	11.3	12.1	1.0
5	47.7	2.9	25.5	13.7
10	32.0	2.7	38.2	7.9
15	19.5	4.9	43.5	19.8
20	17.9	7.4	32.6	20.2
30	16.0	4.1	31.0	7.9
40	14.6	1.3	22.7	9.5
50	7.6	1.4	19.6	1.0

*Concentrations are expressed as area under the HPLC curve .times. 10

DETD **Sildenafil** hydrochloride 15 g
0.05M Phosphate Buffer, pH 4.4 100 ml
Sodium chloride q.s. ad isotonicity

DETD The **sildenafil** is dissolved in the buffer and sufficient sodium chloride is added to the solution to make it isotonic. The solution is placed in a nasal administrator designed to deliver 100 .mu.l of spray for each application. One spray in each nostril will deliver a total of 30 mg of **sildenafil** hydrochloride.

DETD **Sildenafil** hydrochloride 15 g
Methocel 3 g
0.05M Acetate buffer, pH 4.4 100 g

DETD Approximately 70 g of buffer is heated to 80.degree. C., and the methocel is dispersed in it with stirring. The **sildenafil** hydrochloride is dissolved in 30 g of buffer at 80.degree. C., and the

solution is mixed with the methocel dispersion. The resultant mixture is allowed to stand at room temperature for 3 hours. The gel is placed in an ointment tube equipped with a fine orifice and is applied in the nasal nares with a finger or cotton tipped applicator.

DETD

Sildenafil hydrochloride	15 g
Apomorphine hydrochloride	500 mg
0.05M Phosphate Buffer, pH 4.4	100 ml
Sodium chloride	q.s. ad isotonicity

DETD The **sildenafil** hydrochloride and apomorphine hydrochloride are dissolved in the buffer and sufficient sodium chloride is added to the solution to make it isotonic. The solution is placed in a nasal administrator designed to deliver 100 .mu.l of spray for each application. One spray in each nostril will deliver a total of 30 mg of **sildenafil** hydrochloride and 1 mg of apomorphine hydrochloride.

DETD

Sildenafil hydrochloride	15 g
Apomorphine hydrochloride	500 mg
Methocel	3 g
0.05M Acetate buffer, pH 4.4	100 g

DETD Approximately 70 g of buffer is heated to 80.degree. C., and the methocel is dispersed in it with stirring. The **sildenafil** hydrochloride and apomorphine hydrochloride are dissolved in 30 g of buffer at 80.degree. C., and the solution is mixed with the methocel dispersion. The resultant mixture is allowed to stand at room temperature for 3 hours. The gel is placed in an ointment tube equipped with a fine orifice and is applied in the nasal nares with a finger or cotton tipped applicator.

CLM What is claimed is:

1. A method for rapidly and reliably delivering **sildenafil** to the systemic circulation of a patient for the treatment of erectile dysfunction comprising intranasally administering an effective amount of a pharmaceutical composition comprising **sildenafil**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

2. A method according to claim 1, wherein the pharmaceutically acceptable salt of **sildenafil** is **sildenafil** HCl.

4. A method according to claim 1, wherein **sildenafil** is combined with apomorphine or a pharmaceutically acceptable salt thereof.

5. A method according to claim 1, wherein **sildenafil** is combined with one or more vasoactive drugs selected from the group consisting of phenoxybenzamine, phentolamine, papaverine, and pharmaceutically acceptable salts thereof.

6. A method for treating erectile impotence comprising intranasally administering to a patient in need of such treatment an effective amount of **sildenafil**, or a pharmaceutically acceptable salt thereof.

7. A method according to claim 6, wherein **sildenafil** is combined with one or more vasoactive drugs selected from the group consisting of phenoxybenzamine, phentolamine, papaverine, and pharmaceutically acceptable salts thereof.

8. A method according to claim 6, wherein the wherein the pharmaceutically acceptable salt of **sildenafil** is **sildenafil** HCl.

9. A method according to claim 7, wherein the **sildenafil**, or a pharmaceutically acceptable salt thereof is carrier is aqueous.

10. A pharmaceutical composition suitable for intranasal administration comprising **sildenafil**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically and intranasally acceptable carrier therefor.

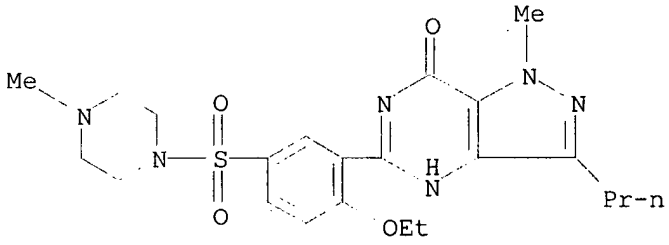
12. A composition according to claim 7, wherein the pharmaceutically acceptable salt of **sildenafil** is **sildenafil** HCl.

IT 50-60-2, Phentolamine 58-74-2, Papaverine 59-96-1, Phenoxybenzamine **139755-83-2**, Sildenafil **171599-83-0**, Sildenafil citrate **252920-86-8**
(nasal administration of sildenafil and vasoactive drugs for treatment of erectile dysfunction)

IT **139755-83-2**, Sildenafil **171599-83-0**, Sildenafil citrate **252920-86-8**
(nasal administration of sildenafil and vasoactive drugs for treatment of erectile dysfunction)

RN 139755-83-2 USPATFULL

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl- (9CI) (CA INDEX NAME)



RN 171599-83-0 USPATFULL

CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 139755-83-2
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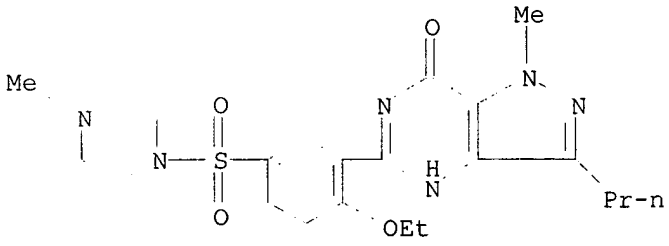
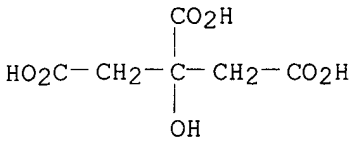
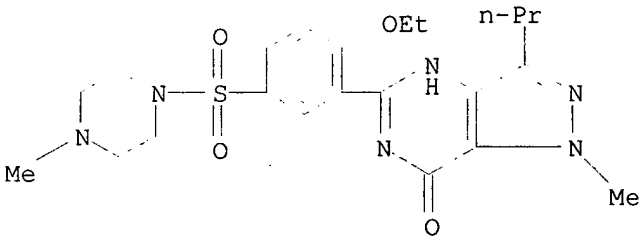


CM 2

CRN 77-92-9
CMF C6 H8 O7



RN 252920-86-8 USPATFULL
CN Piperazine, 1-[[3-(4,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L95 ANSWER 17 OF 17 USPAT2
AN 2002:16611 USPAT2
TI Methods and transdermal compositions for pain relief
IN Murdock, Robert W., Selah, WA, United States
Williams, C. Donald, Yakima, WA, United States
PA Pharmaceutical Applications Associates LLC, Yakima, WA, United States (U.S. corporation)
PI US 6479074 B2 20021112
AI US 2001-825375 20010402 (9)
RLI Division of Ser. No. US 2000-652662, filed on 31 Aug 2000 Division of Ser. No. US 1999-342679, filed on 29 Jun 1999, now abandoned Continuation-in-part of Ser. No. US 1998-106684, filed on 29 Jun 1998, now patented, Pat. No. US 6290986 Continuation-in-part of Ser. No. WO 1997-US19651, filed on 24 Oct 1997 Continuation-in-part of Ser. No. US 1997-957485, filed on 24 Oct 1997, now abandoned
PRAI US 1999-122903P 19990305 (60) <--
US 1996-29120P 19961024 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala, Lakshmi S.
LREP Lahive & Cockfield LLP, DeConti, Giulio A., Laccotripe, Maria C.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 1775
AB The present invention features methods and compositions for transdermal administration. In one embodiment, the invention features methods and compositions for transdermal administration of an amine containing compound having biphasic solubility and/or an agent which enhances the activity of the amine containing compound having biphasic solubility, e.g., a muscle relaxant, to relieve pain.

PRAI US 1999-122903P 19990305 (60) <--

PRAI US 1996-29120P 19961024 (60) <--

DETD As used herein, the term "pain" is art recognized and includes a bodily sensation elicited by noxious chemical, mechanical, or thermal stimuli, in a subject, e.g., a mammal such as a human. The term "pain" includes chronic pain, such as lower back pain; pain due to arthritis, e.g., osteoarthritis; joint pain, e.g., knee pain or carpal tunnel syndrome; myofascial pain, and **neuropathic** pain. The term "pain" further includes acute pain, such as pain associated with muscle strains and sprains; tooth pain; headaches; pain associated with surgery; or pain associated with various forms of tissue injury, e.g., inflammation, infection, and ischemia.

DETD In yet a further embodiment of the invention, the pharmaceutical compound is a compound used in the treatment of impotence such as **sildenafil**, sold under the tradename **Viagra**. It is believed that transdermal administration of **sildenafil** may be useful, for at least some subjects, as compared to oral administration which has been found, in at least some situations, to be associated with gastrointestinal side effects.

DETD 0.15 grams **sildenafil** was crushed and strained and dissolved in 5 milliliters Pluronic 20% F127 and mixed between syringes. 2.2 milliliters of soya lecithin was added and mixed. Sufficient Pluronic 20% was added to yield 10 milliliters and the resultant composition was mixed well to yield a composition having the strength of about 15 milligrams per milliliter.

DETD A mixture of **Sildenafil** 15 mg/ml was applied to the penis and scrotum of a 51 year old male. An immediate and strong erection resulted with sexual stimulation, without any irritation or burning. It is believed the composition will possess the therapeutic results claimed for orally administered **Sildenafil**, without any time delay, without any systemic GI side effects, and possibly without the degree of drug interaction with nitrates used in cardiac disease. It is believed that this will contribute both to the convenience of use of the pharmaceutical and to its safety.

DETD Doxepin appears to provide about three times the positive response rate compared to at least some other pharmaceutical agents described herein, regardless of whether such other pharmaceutical agents are administered singly or in combination. Doxepin appears to be substantially more effective than amitriptyline as a pain, e.g., **neuropathic** pain agent when administered transdermally. This appears to be true regardless of whether doxepin is administered as a single agent or is administered in combination with other pharmaceuticals as described herein.

DETD Carbamazepine appears to provide positive effects as a pain, e.g., **neuropathic** pain agent, at least in properly selected patients. Carbamazepine appears to cause a rash in at least some patients, requiring its discontinuation.

=> d his

(FILE 'HOME' ENTERED AT 15:40:11 ON 26 FEB 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:40:28 ON 26 FEB 2003
L1 25559 S N2C3-NCNC3/ES AND 46.150.18/RID
L2 30 S L1 AND C22H30N6O4S
L3 9 S L2 AND 1/NC
L4 5 S L3 AND 4 ETHOXYPHENYL
L5 4 S L4 AND 4 METHYL
SEL RN 1 4
L6 2 S E1-E2
L7 1 S L6 NOT METHYLSULFONYL
SEL RN

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L8          19 S E3/CRN
L9             STR
L10         30 S L9
L11        690 S L9 FUL
               SAV L11 JKIM088/A TEMP
L12        670 S L11 NOT L7,L8
L13            STR L9
L14         14 S L13 CSS SAM SUB=L11
L15        324 S L13 CSS FUL SUB=L11
               SAV L15 JKIM088A/A TEMP
L16            STR L13
L17        235 S L16 CSS FUL SUB=L15
               SAV L17 JKIM088B/A TEMP
L18            STR L16
L19         55 S L18 CSS FUL SUB=L17
               SAV L19 JKIM088C/A TEMP
L20         35 S L19 NOT L7,L8
L21         82 S L15 AND NC2NC2/ES
L22         50 S L21 NOT L19,L7,L8
L23         42 S L22 AND S/ELS
L24         24 S L23 AND 4/NR NOT P/ELS
L25          4 S L24 AND (C24H34N6O5S OR C24H32N6O5S OR C22H30N6O5S OR C21H28N
L26          3 S L24 AND 2/NC
L27          1 S L26 NOT I/ELS
L28          5 S L25,L27
L29         19 S L24 NOT L28
L30          1 S L29 AND C23H32N6O5S
L31          6 S L28,L30
L32          7 S L15 AND NCNC2/ES
L33          3 S L32 AND (C21H24N6O4S OR C21H24N6O2 OR C20H22N6O2)
L34         44 S L20,L31,L33
L35         42 S L34 NOT NC6/ES
L36            STR L13
L37         13 S L36 CSS FUL SUB=L15
               SAV L37 JKIM088D/A TEMP
L38            STR L36
L39          0 S L38 CSS FUL SUB=L15
               SAV L39 JKIM088E/A
L40            STR L36
L41         18 S L40 CSS FUL SUB=L15
               SAV L41 JKIM088F/A TEMP
L42         71 S L35,L37,L41
L43        176 S L17 NOT L7,L8,L42
L44        173 S L43 AND 1/NC
L45        152 S L44 NOT P/ELS
L46        140 S L45 AND NR<=4
L47         12 S L45 NOT L46
L48        114 S L46 NOT (46.150.1 OR 46.156.30)/RID
L49        113 S L48 NOT C5/ES
L50         17 S L49 AND 3/NR
L51          7 S L50 AND (C21H29N5O4S OR C19H25N5O4S OR C22H31N5O4S OR C20H27N
L52         78 S L42,L51

    FILE 'HCAPLUS' ENTERED AT 17:38:01 ON 26 FEB 2003
L53         56 S L52
L54        561 S L7 OR L8
L55        694 S SILDENAFIL OR SILDENAFIL (S) CITRATE OR VIAGRA
L56        710 S L54,L55
               E LAREIDA J/AU
L57          2 S E4
L58          0 S L57 AND L53
L59          1 S L57 AND L56
               E NEUROPATHY/CT
```

```
                E E3+ALL
L60          3180 S E2
                E NERVE DISEASE/CT
                E E4+ALL
L61         13810 S E2
L62          3373 S E2 (L) NEUROPATH?
                E NERVOUS SYSTEM AGENTS/CT
L63        157909 S E3+NT
                E E3+ALL
L64           380 S E4
L65        272341 S E183+NT
                E NERVE/CT
L66        130930 S E3+NT
L67            10 S L53 AND L60-L66
L68           105 S L56 AND L60-L66
L69             9 S L68 AND NEUROPATH?
L70             1 S L59 AND L60-L69
L71             8 S L69 NOT L70
L72             7 S L71 NOT GENE/TI
L73             8 S L70,L72
L74             4 S L67 AND NEUROPATH?
L75             9 S L73,L74
L76             8 S L68 AND L60
L77             8 S L68 AND L62
L78             8 S L68 AND L61
L79            10 S L75-L78
L80             9 S L79 AND L56
L81             1 S L79 NOT L80
L82             6 S L67 NOT L79

     FILE 'REGISTRY' ENTERED AT 17:59:54 ON 26 FEB 2003
L83             1 S L8 AND VIAGRA

     FILE 'HCAPLUS' ENTERED AT 18:00:29 ON 26 FEB 2003
L84            10 S L79-L81

     FILE 'USPATFULL, USPAT2' ENTERED AT 18:02:56 ON 26 FEB 2003
L85           143 S L7 OR L8
L86            35 S L52
L87           409 S L55
L88           430 S L85-L87
L89            58 S L88 AND ?NEUROPATH?
                E NEUROPATHY/CT
L90            18 S E3
                E NERVE, DISEASE/CT
L91          1513 S E3,E4
L92             0 S L88 AND L90
L93             9 S L88 AND L91
L94            58 S L89,L93
L95            17 S L94 AND (PD<=19991012 OR PRD<=19991012)

     FILE 'USPATFULL, USPAT2' ENTERED AT 18:05:02 ON 26 FEB 2003

     FILE 'MEDLINE' ENTERED AT 18:06:19 ON 26 FEB 2003
L96          1056 S L7 OR L8
L97             0 S L52
L98          1302 S L55
L99            13 S L96,L98 AND ?NEUROPATH?
                E NEUROPATHY/CT
                E E15+ALL
L100         9083 S E2+NT
                E NEUROPATH/CT
                E E5+ALL
```

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L101        4454 S E2
L102          46 S E7
L103         340 S E12
L104         606 S E14
L105          22 S E16
L106         402 S E22
L107         214 S E24
L108          57 S E26
L109        2278 S E28
L110          57 S E30
L111          56 S E36
L112        6820 S E38
L113         353 S E40
L114          57 S E42
L115         611 S E44
L116          49 S E46
L117          40 S E50
L118          57 S E52
L119         590 S E54
L120         375 S E56
L121         375 S E58
L122          58 S E60
L123         123 S E62
L124          20 S E64
L125         352 S E66
L126          20 S E68
L127          57 S E70
L128          20 S E72
L129          20 S E74
L130          56 S E76
L131        2278 S E78
L132         504 S E80
L133        3304 S E82
L134        7466 S E84
L135          45 S E86
L136          45 S E88
L137          57 S E90
L138          20 S E92
L139          56 S E94
L140          57 S E96
L141         147 S E98
L142         402 S E100
L143         920 S E102
L144          57 S E104
L145         340 S E106+NT
L146          20 S E110
L147         266 S E112
L148         844 S E114
L149         814 S E116
L150         123 S E118
L151          55 S E120
L152          76 S E122
L153          56 S E124
L154          62 S E126
L155          10 S L96,L98 AND L100-L154
                 E NERVE DISEASE/CT
                 E E6+ALL
                 E E2+ALL
L156          78 S C10./CT AND L96,L98
L157          10 S L99,L155 AND L156
L158          16 S L99,L155,L157
L159           1 S L158 AND PY<=1999
L160          17 S L156 AND PY<=1999
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L161         17 S L159,L160

=> fil wpix
FILE 'WPIX' ENTERED AT 18:17:34 ON 26 FEB 2003
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FILE LAST UPDATED:          24 FEB 2003      <20030224/UP>
MOST RECENT DERWENT UPDATE:     200313        <200313/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


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    /BIX is also provided which comprises both /BI and /ABEX <<<

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    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d que

L162        182 SEA FILE=WPIX ABB=ON  PLU=ON  (SILDENAFIL/BIX OR SILDENAFIL/BIX
                (S) CITRATE/BIX OR VIAGRA/BIX)
L163          5 SEA FILE=WPIX ABB=ON  PLU=ON  L162 AND ?NEUROPATH?/BIX


=> d all abeq tech abex tot

L163 ANSWER 1 OF 5  WPIX (C) 2003 THOMSON DERWENT
AN   2002-164493 [21]   WPIX
DNC  C2002-050808
TI   Treatment of e.g. diseases related to peripheral vascular disease,
     peripheral neuropathies and autonomic neuropathies
     comprises administration of cyclic guanosine 3',5'-monophosphate type five
     inhibitors.
DC   B04
IN   WOOD, R E
PA   (WOOD-I) WOOD R E
CYC  96
PI   WO 2002002118 A1 20020110 (200221)* EN   16p    A61K031-495
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TR TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU
            SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
```

AU 2001079275 A 20020114 (200237) A61K031-495
ADT WO 2002002118 A1 WO 2001-US41202 20010629; AU 2001079275 A AU 2001-79275 20010629
FDT AU 2001079275 A Based on WO 200202118
PRAI US 2000-219029P 20000718; US 2000-215065P 20000630
IC ICM A61K031-495
AB WO 200202118 A UPAB: 20020403
NOVELTY - Treatment of peripheral vascular diseases, peripheral **neuropathies**, autonomic **neuropathies**, onychiomycosis or treating or preventing diabetic foot ulcers involves administering a composition comprising cyclic guanosine 3',5'-monophosphate type 5 (cGMP PDE5) inhibitor or its salt.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for manufacturing a diabetic foot ulcer therapeutic involving providing the cGMP PDE5 inhibitor or its salt and combining with a carrier.

ACTIVITY - Vasotropic; Antirheumatic; Antidiabetic; Ophthalmological; Antiulcer; Fungicide.

A patient having an insulin dependent diabetes and suffering from erectile dysfunction and a diabetic foot ulcer. Once **sildenafil** treatment had began for his erectile dysfunction, it was noted that the ulcer was decreasing in the size and the patient was instructed to begin taking 50 mg of **sildenafil** once a day. This resulted in complex resolution of the diabetic foot ulcer in one month and the patient had continued on this treatment for the past two years without reoccurrence.

MECHANISM OF ACTION - cGMP PDE5 inhibitor.

USE - For treating peripheral vascular disease, peripheral **neuropathies** and autonomic **neuropathies** e.g. Raynaud's phenomenon, CREST syndrome, erythromatosis, rheumatoid diseases and diabetic retinopathies; onychiomycosis (fungal infection of the nailbed); and diabetic foot ulcer, (all claimed); and disease resulting from small vessel and large vessel disease erectile dysfunction.

ADVANTAGE - The CGMP PDE5 inhibitor, particularly **sildenafil** enhances the blood supply to the ulcerated limb and thus enhances the rate of heating in diabetic foot ulcer. The CGMP PDE5 inhibitor provides prophylactic to diabetics predisposed to diabetic ulcers and thus save from suffering the deleterious effects and possibility of limb amputations. The inhibitor achieves unexpected rapid and complete healing of their foot ulcers.

Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B06-D09; B14-A04; B14-C06; B14-D07A; B14-F02D; B14-F02F; B14-J01; B14-J02; B14-N03; B14-N17
ABEX

SPECIFIC COMPOUNDS - **Sildenafil** is specifically claimed as the cGMP PDE5 inhibitor.

ADMINISTRATION - The cGMP PDE5 inhibitor administered orally, parenterally, rectally or transdermally (e.g. topically) in the dosage of 0.5 - 400 (preferably 25 - 100)mg/day, three times day.

EXAMPLE - No relevant example is given

L163 ANSWER 2 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN 2002-049127 [06] WPIX
DNC C2002-013722
TI New 8-quinolinxanthine and 8- isoquinolinxanthine derivatives useful in the treatment of e.g. sexual dysfunction.
DC B02
IN BHALAY, G; COLLINGWOOD, S P; FAIRHURST, R A; GOMEZ, S F; NAEF, R; SANDHAM, D A
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH
CYC 96

PI WO 2001077110 A1 20011018 (200206)* EN 70p C07D473-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001073921 A 20011023 (200213) C07D473-06
NO 2002004741 A 20021002 (200304) C07D473-06
CZ 2002003305 A3 20030115 (200309) C07D473-06
EP 1268480 A1 20030102 (200310) EN C07D473-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2001077110 A1 WO 2001-EP3909 20010405; AU 2001073921 A AU 2001-73921 20010405; NO 2002004741 A WO 2001-EP3909 20010405, NO 2002-4741 20021002; CZ 2002003305 A3 WO 2001-EP3909 20010405, CZ 2002-3305 20010405; EP 1268480 A1 EP 2001-940294 20010405, WO 2001-EP3909 20010405

FDT AU 2001073921 A Based on WO 200177110; CZ 2002003305 A3 Based on WO 200177110; EP 1268480 A1 Based on WO 200177110

PRAI GB 2000-8694 20000407

IC ICM C07D473-06
ICS A61K031-52; A61P015-00; C07D239-54

AB WO 200177110 A UPAB: 20020128
NOVELTY - 8-Quinolinxanthine and 8- isoquinolinxanthine derivatives are new.

DETAILED DESCRIPTION - 8-Quinolinxanthine and 8- isoquinolinxanthine derivatives of formula (I) or their salts are new.

R1 and R3 = H or alkyl optionally substituted by OH, alkoxy, or alkylthio;

R2 = H, alkyl, hydroxyalkyl, alkylcarbonyloxyalkyl, alkoxyalkyl, alkylthioalkyl, alkenyl, cycloalkylalkyl, heterocyclylalkyl or aralkyl (where the aryl ring is optionally fused to a 5-membered heterocyclic group or is optionally substituted by at least one substituent selected from alkoxy, NH2, alkylamino, dialkylamino, acylamino, halo, OH, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino or dialkylaminosulfonylamino);

R4 = H or alkyl;

R5 = quinolinyl, isoquinolinyl or oxodihydroisoquinolinyl (optionally fused to a 5-membered heterocyclic group and optionally substituted by at least one substituent selected from halo, CN, OH, alkyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, alkoxy, alkylthio, alkenyl, alkoxycarbonyl, alkynyl, carboxyl, acyl, N(R6)R7, aryl (optionally substituted by at least one substituent selected from halo or alkoxy), or heteroaryl having 5 or 6 ring atoms attached through a ring carbon atom to the indicated carbon atom);

R6 and R7 = H or alkyl optionally substituted by OH or alkoxy or one of R6 and R7 is H and the other is acyl; and

N(R6)(R7) = 5- or 6- membered heterocyclyl group.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition comprising (I) optionally with a diluent or carrier;

(2) preparation of (I); and

(3) a compound of formula (II).

ACTIVITY - Vasotropic; Tocolytic; Gynecological; Analgesic; Cytostatic; Uropathic; Antianginal; Hypotensive; Cardiant; Antiarteriosclerotic; Antiinflammatory; Antiasthmatic; Antiallergic; Opthalmological; Immunomodulator; Dermatological; Neuroprotective; Antidiabetic; Cerebroprotective; Nootropic; Antipsoriatic.

MECHANISM OF ACTION - Phosphodiesterase (PDE5) inhibitor.

A 10 mM solution of 8-(6,7-dimethoxy-quinolin-4-ylmethyl)-3-isobutyl-1-methyl-3,7-dihydro-purine-2,6-dione (B) in dimethyl sulfoxide (DMSO) was diluted with aqueous DMSO (20 vol/vol%) to give stock solution (100 micro M). The solution was transferred to a well and DMSO or **sildenafil**

solution was added an assay mix (80 micro l) prepared by mixing PDE assay buffer (2 ml), an aqueous solution of bovine serum albumin (BSA) containing 5 mg BSA/ml (2 ml), an aqueous 75 micro M solution of cyclic guanosine-3',5'-monophosphate (cGMP) sodium salt (0.2 ml), 3H-c-GMP (10 micro l) and distilled water (11.8 ml). A solution of human PDE5 in 20 mM hepes, pH 7.4, sodium chloride (100 mM), glycerol (10 vol/vol%), benzamidine (1 mM) and dithiotherietol (2 mM) was diluted with enzyme buffer prepared by adding 0.5 M ethylene diamine tetra acetic acid (EDTA) (2 ml) to a solution of tris-base (1.21 g) in water (800 ml), adjusting the pH to 7.5. The diluted PDE5 solution (10 micro l) was added to the well. The plate was incubated at room temperature for 1 hour. 50 micro l of a suspension of 500 mg PDE Yttrium silicate SPA beads in 28 ml water was added to the well and the plate was incubated for a further 20 minutes and then sealed. The concentration of (B) at which 50% inhibition of PDE5 to the beads occurred was found to be between 0.0005 micro M and 10 micro M.

USE - For manufacture of a medicament for treatment of conditions mediated by PDE5 e.g. sexual dysfunction, including male erectile dysfunction (claimed) and female sexual dysfunction, premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, bronchitis, asthma, allergic rhinitis, glaucoma, tinnitus, diseases characterized by disorders of gut motility, e.g. irritable bowel syndrome, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic **neuropathy**, stroke, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker esophagus, anal fissure and hypoxic vasoconstriction.

ADVANTAGE - (I) exhibits good selectivity for the inhibition of PDE5 relative to inhibition of other phosphodiesterases particularly PDE1 and PDE6, indicating a low side-effect profile.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-D09; B06-H; B07-D12; B07-H; B14-E10; B14-F01; B14-F01D; B14-F02B; B14-F07; B14-H01B; B14-J01A4; B14-K01; B14-N02; B14-N04; B14-N14; B14-N16; B14-R02; B14-S01

TECH UPTX: 20020128

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) in free or salt form involves either:

(a) dehydrating a compound of formula (II); or

(b) preparation of (I) in free or salt form (where R3 is alkyl optionally substituted by OH, alkoxy or alkylthio) involves reacting (I) in free or salt form with an appropriate alkylating agent; or

(c) preparation of (I) in free or salt form (where R2 is aralkyl substituted in the aryl ring by alkylsulfonylamino or dialkylaminosulfonylamino) involves reacting (I) in free or salt form (where R2 is aralkyl substituted by NH2) with an alkylsulfonyl halide or dialkylaminosulfonyl halide; or

(d) preparation of (I) in free or salt form (where R2 is hydroxy-substituted alkyl), hydration of (I) (where R2 is alkenyl); or

(e) preparation of (I) in free or salt form (where R2 is alkyl substituted by alkylcarbonyloxy), appropriate esterification of (I) where R2 is hydroxy-substituted alkyl); or

(f) preparation of (I) in free or salt form (where R2 is aralkyl substituted in the aryl ring by NH2), hydrolysing (I) (where R2 is aralkyl substituted in the aryl ring by acylamino); or

(g) preparation of (I) in free or salt form (where R5 is quinolinyl or isoquinolinyl substituted by OH), dealkylation of (I) (where R5 is quinolinyl or isoquinolinyl substituted by alkoxy); or

(h) preparation of (I) in free or salt form (where R5 is quinolinyl or isoquinolinyl substituted by halo), halogenation of (I) (where R5 is quinolinyl or isoquinolinyl having an unsubstituted ring carbon atom); or (i) preparation of (I) in free or salt form (where R2 is a cyclopropyl group, optionally substituted by alkyl), subjecting (I) (where R2 is alkenyl) to a Simmons Smith cyclopropanation reaction.

ABEX

SPECIFIC COMPOUNDS - 10 Compounds are specifically claimed as (I) e.g. 8-(6,7-dimethoxy-quinolin-4-ylmethyl)-3-isobutyl-1-methyl-3,7-dihydro-purine-2,6-dione of formula (Ia).
ADMINISTRATION - (I) can be administered orally, parenterally (e.g. intravenously, intramuscularly, intracavernosally or subcutaneously), intranasally, by inhalation, buccally, sublingually, topically or rectally.

EXAMPLE - Lithium diisopropylamide (2.46 ml) and potassium tert-butoxide (0.552 g) were added to tetrahydrofuran (10 ml) at -70degreesC, followed by the addition of 6,7-dimethoxy-4-methyl-quinoline (1.0 g). After 1 hour the reaction mixture was poured on to an excess of crushed ice and warmed to room temperature overnight. Pyridine hydrochloride (0.57 g) was added and the reaction partitioned. The aqueous phase was evaporated, taken into hot methanol, treated with charcoal, filtered and evaporated to afford (6,7-dimethoxy-quinolin-4-yl)-acetic acid (A). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.33 ml) was added to a suspension of 5,6-diamino-1-isobutyl-3-methyl-1H-pyrimidine-2,4-dione (0.327 g), (A) (0.41 g) and 1-hydroxybenzotriazole (0.251 g) in dichloromethane (2 ml). Water (2 ml) was added, the biphasic mixture was shaken for 18 hours and the resultant solid was collected by filtration. The intermediate was suspended in methanol (10 ml), 4M aqueous sodium hydroxide (5 ml) was added and the mixture heated to reflux for 4 hours. After work up 8-(6,7-dimethoxy-quinolin-4-ylmethyl)-3-isobutyl-1-methyl-3,7-dihydro-purine-2,6-dione was obtained.

DEFINITIONS - Preferred Definitions:
R1, R3 and R4 = H or 1-4C alkyl;
R2 = H, 1-8C alkyl, hydroxy-1-8C-alkyl, 1-4C alkylcarbonyloxy-1-8C-alkyl, 2-4C alkenyl, 3-6C-cycloalkyl-1-4C alkyl, heterocyclyl-1-4C (where the heterocyclyl group is a 5- membered heterocyclyl group having one N or O in the ring) or phenyl-1-4C-alkyl (where the phenyl ring is optionally mono- or di-substituted with 1-4C-alkoxy, NH2, 1-4C alkylcarbonylamino, Cl, Br, 1-4C alkylsulfonylamino or di(1-4C alkyl)aminosulfonylamino and is optionally fused to a 5-membered heterocyclic ring having two oxygen atoms in the ring);
R5 = an isoquinolinyl substituted at 1, 3, 5, 6, 7 and 8 positions by R8, R9, R10, R11, R12 and R13;
R8 = H, 1-4C alkyl, halo, CN or -N(R6)(R7);
R6 and R7 = 1-4C alkyl;
N(R6)(R7) = 6-membered heterocyclyl group having one or two N or one N and one O in the ring or phenyl mono- or di-substituted with 1-4C alkoxy;
R9 and R10 = H, 1-4C alkyl or halo;
R11 and R12 = H, halo, CN, carboxy, OH, 1-4C alkyl, 1-4C alkoxy or 2-4C alkynyl;
C(R11)(R12) = 5-membered heterocycle having two O atoms in the ring; and
R13 = H or halo.

L163 ANSWER 3 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN 2001-381956 [41] WPIX
DNC C2001-117060
TI Treatment of **neuropathy**, especially diabetic **polyneuropathy**, comprises administering a cyclic guanosine monophosphate phosphodiesterase 5 inhibitor.
DC B04
IN GROSSMAN, E B; KOPPIKER, N P; LEICHTER, S B

PA (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD
CYC 32
PI AU 2000066650 A 20010426 (200141)* 30p A61P025-02
CA 2323839 A1 20010421 (200141) EN A61K031-519
JP 2001122803 A 20010508 (200142) 15p A61K045-00
EP 1129706 A2 20010905 (200151) EN A61K031-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001051181 A 20010625 (200172) A61K031-522
ZA 2000005825 A 20020626 (200251) 27p A61K000-00
NZ 507690 A 20021025 (200274) A61K031-505
HU 2000004120 A2 20021128 (200309) A61K031-519
ADT AU 2000066650 A AU 2000-66650 20001020; CA 2323839 A1 CA 2000-2323839 20001019; JP 2001122803 A JP 2000-322510 20001023; EP 1129706 A2 EP 2000-309129 20001017; KR 2001051181 A KR 2000-62129 20001021; ZA 2000005825 A ZA 2000-5825 20001019; NZ 507690 A NZ 2000-507690 20001020; HU 2000004120 A2 HU 2000-4120 20001020
FDT NZ 507690 A Div in NZ 521313
PRAI GB 2000-21520 20000901; GB 1999-24958 19991021
IC ICM A61K000-00; A61K031-00; A61K031-505; A61K031-519; A61K031-522; A61K045-00; A61P025-02
ICS A61K031-33; A61P003-10; A61P025-00; A61P043-00; C07C000-00
ICA C07D487-04
AB AU 200066650 A UPAB: 20010724
NOVELTY - Treatment of **neuropathy** comprises administering a cyclic guanosine monophosphate phosphodiesterase 5 (cGMP PDE5) inhibitor (I), provided that (I) is not a substituted 5-(3-pyridyl)-pyrazolo(4,3-d)pyrimidin-7-one, 2-(3-pyridyl)-4a,5-dihydro-imidazo(5,1-f)(1,2,4)triazin-4(3H)-one, 2-phenyl-6-purinone or 2-(3-pyridyl)-6-purinone for treating diabetic **neuropathy**.
ACTIVITY - Neuroprotective; antidiabetic; analgesic.
MECHANISM OF ACTION - cGMP PDE5 inhibitor.
USE - The method is especially useful for treating diabetic **polyneuropathy**. Men with symptoms of diabetic **neuropathy** were treated with **sildenafil** (50 mg) every night for 10 days. The results (not given) demonstrated a reduction in the degree of pain experienced by a number of patients.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B06-D09; B14-J01; B14-S04
TECH UPTX: 20010724
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred cGMP PDE5 Inhibitor: (I) has an IC50 of less than 100 nM and a selectivity ratio of more than 1000 (preferably over PDE3 and PDE4).
ABEX
SPECIFIC COMPOUNDS - (I) is **sildenafil** (5-(2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)phenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one).

ADMINISTRATION - (I) is administered orally at daily doses of 5-500 mg, especially 10-100 mg.

L163 ANSWER 4 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN 2001-281821 [29] WPIX
DNC C2001-085754
TI Medicament for treating **neuropathy** e.g. diabetic **polyneuropathy** or gastroparesis, contains phenyl-pyrazolo-pyrimidinone derivatives, preferably **sildenafil**.
DC B02
IN LAREIDA, J
PA (LARE-I) LAREIDA J
CYC 82

PI WO 2001026659 A1 20010419 (200129)* DE 19p A61K031-505
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 2000058009 A 20010423 (200147) A61K031-505
EP 1220672 A1 20020710 (200253) DE A61K031-505
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

ADT WO 2001026659 A1 WO 2000-CH409 20000727; AU 2000058009 A AU 2000-58009 20000727; EP 1220672 A1 EP 2000-943518 20000727, WO 2000-CH409 20000727

FDT AU 2000058009 A Based on WO 200126659; EP 1220672 A1 Based on WO 200126659

PRAI CH 1999-1862 19991012

IC ICM A61K031-505
ICS A61P025-00

AB WO 200126659 A UPAB: 20010528
NOVELTY - Medicament for treating **neuropathy** contains 5-phenyl-pyrazolo (4,5-d) pyrimidin-7(6H)-one derivatives (I).

DETAILED DESCRIPTION - Medicament for treating **neuropathy** contains pyrazolo-pyrimidine compounds of formula (I) or their salts.

R1 = 1-6C alkyl (optionally substituted (os) by halo);
R2 = H, 1-4C alkyl (os by halo) or halo;
R3 = 2-4C alkyl (os by halo);
R4 = CO2NR5R6, 1-4C alkyl (os by NR5R6, CN, CONR5R5, COOR7 or halo), 2-4C alkenyl (os by NR5R6, SO2NR5R6, CONR5R5, COOR7 or halo) or 2-4C alkanoyl (os by NR5R6, SO2NR5R6, CONR5R5, COOR7 or halo);
R5, R6 = H or 1-4C alkyl, or
NR5R6 = pyrrolidino, piperidino, morpholino, N-(R8)-piperazino or 1-imidazolyl (os by 1 or 2 1-4C alkyl);
R7 = H or 1-4C alkyl (os by F), and
R8 = H, 1-3C alkyl or 1-4C hydroxyalkyl.

ACTIVITY - Neuroprotective; antidiabetic.

MECHANISM OF ACTION - Cyclic guanosine 3',5'-monophosphate diesterase (cGMP PDE) inhibitor.

USE - (I) are useful for treating peripheral diabetic **polyneuropathy**, gastroparesis, general degenerative, toxic, metabolic or ischemic **neuropathy** and other autonomous forms of **neuropathy**. (I) are known selective cGMP PDE inhibitors, previously used for treating cardiovascular diseases (see EP463756); in particular the preferred compound **sildenafil** (Ia) has previously been used for treating erectile dysfunction.

(Ia) was administered at 50 mg (one tablet) per week to a 66 year old male Type II diabetes mellitus patient showing the symptoms of diabetic **polyneuropathy**. After 12 month of treatment the neurological condition of the patient was normalized, as shown e.g. by heat-cold differentiation ability.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-D09; B14-E10; B14-F01B; B14-F09; B14-J01; B14-S04

TECH UPTX: 20010528
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) Are prepared e.g. as described in EP463756, WO9307149, WO9306104 or WO9405661.

ABEX
SPECIFIC COMPOUNDS - Use of one compound (I) is specifically claimed i.e: **sildenafil** (Ia).

ADMINISTRATION - The dose is 1-100 (preferably 5-50) mg/day, typically 25-50 mg/week.

DEFINITIONS - Preferred definitions:
R4 = 4-(1-4C alkyl)-piperazinosulfonyl.

L163 ANSWER 5 OF 5 WPIX (C) 2003 THOMSON DERWENT
AN 2001-138727 [14] WPIX
DNC C2001-041066
TI Methods of increasing optic nerve, choroidal and retinal blood flow to facilitate the preservation of sight.
DC B05
IN SPONSEL, W E
PA (TEXA) UNIV TEXAS SYSTEM
CYC 94
PI WO 2001010406 A2 20010215 (200114)* EN 54p A61K009-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000065365 A 20010305 (200130) A61K009-00
EP 1246605 A2 20021009 (200267) EN A61K009-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001010406 A2 WO 2000-US21929 20000810; AU 2000065365 A AU 2000-65365 20000810; EP 1246605 A2 EP 2000-952721 20000810, WO 2000-US21929 20000810
FDT AU 2000065365 A Based on WO 200110406; EP 1246605 A2 Based on WO 200110406
PRAI US 1999-148150P 19990810
IC ICM A61K009-00
AB WO 200110406 A UPAB: 20011129
NOVELTY - Method for improving visual function and optimizing the health of the optic nerve and retina by increasing blood flow by a composition including an agent that increases cyclic-guanosine monophosphate (cyclic-GMP) levels, either directly, or by stimulating cyclic-GMP synthesis or by inhibiting cyclic-GM selective phosphodiesterase(s).

DETAILED DESCRIPTION - A method for treating an optic nerve disease comprises administering a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of treating retinal disease using above composition;

(2) a method of treating choroidal disease using above composition;

(3) a method for increasing ocular blood flow comprising administering a composition comprising at least a first cyclic-GMP phosphodiesterase inhibitor to a patient suffering from a macular disorder;

(4) a method for treating macular edema, comprising administering a composition containing at least a first agent that increases cyclic-GMP;

(5) a method for inhibiting or preventing the accumulation of lipofuscin in an eye comprising administering a composition comprising at least a first agent that inhibits phosphodiesterase type 5;

(6) a method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that activates guanylate cyclase;

(7) a method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that increases ocular nitric oxide levels;

(8) a kit for treatment of ocular disorders comprising:

(i) a sealed container housing a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP; and

(ii) instructions for administering composition;

(9) a composition for increasing ocular blood flow, comprising at least a first compound that increases ocular levels of cyclic-GMP;

(10) a method for treating optical nerve disease comprising administering **sildenafil citrate**;

(11) a method for treating choroidal disease comprising administering

sildenafil citrate;

(12) a method for increasing visual function comprising administering **sildenafil citrate** to an affected eye;

(13) a method for increasing ocular blood flow comprising administering **sildenafil citrate;**

(14) a method for increasing visual function comprising administering to a patient with normal vision **sildenafil citrate;**

and

(15) an ophthalmic preparation comprising a carrier and **sildenafil citrate** at a concentration of 0.001 - 20 % weight per volume.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - Cyclic-GMP phosphodiesterase inhibitor; guanylate cyclase activator

USE - For the treatment of optical nerve disease from normotensive excavatory optic **neuropathy,** ischemic optic **neuropathy** , toxic optic **neuropathy,** traumatic optical **neuropathy** or idiopathic optic **neuropathy.** The idiopathic optic **neuropathy** may be optic nerve drusen or benign intracranial hypertension. For the treatment of retinal disease including retinal neovascularization, ischemic hematologic/rheologic disorders or toxic maculpathy. For treating choroidal disease, especially when it is an ischemic disorder of the posterior choroid, degenerative subretinal neovascularization, diabetic choroidal ischemia, inflammatory subretinal neovascularization or non-age related choroidal ischemia. The ischemic disorder of the posterior choroid may be degenerative drusen of the macula, macular retinal pigment epithelial atrophy, or retinal pigment epithelial detachment. The degenerative subretinal neovascularization may be wet age related mascular degeneration. Useful for the treatment of mascular disorders including macular edema, macular degeneration, familial drusen, macular disorders due to hypertension, angioma, papillitis, neuroretinitis or pigmentary retinal degenerative disorders. The macular edema is with vascular leakage from diabetic retinopathy, branch retinal vein occlusion, intermediate uveitis or ideopathic retinal telangiectasis.

May also be used for increasing visual function comprising administering **sildenafil citrate** to an affected eye, and may be used for increasing visual function for a patient with normal vision.

Dwg.0/11

FS CPI

FA AB; DCN

MC CPI: B04-A06; B05-A01B; B05-A03A; B05-C03; B06-H; B07-D04C; B07-D10; B10-A03; B10-A05; B10-A12C; B10-A19; B14-D07A; B14-F02D; B14-N03

TECH UPTX: 20010312

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred agent: The agent is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator. The cyclic-GMP phosphodiesterase inhibitor is from **sildenafil**, dipyridamole, zaprinast, filaminast, denbufyllene, piclamilast, zardaverine, a carboline derivative, a pyridocarbazole derivative or a quinozolinone compound. The guanylate cyclase activator is from sodium azide, sodium nitrite, hydroxylamine, hydrazines, nitroglycerine, nitroprusside, nitrosureas or nitrosamines. The phosphodiesterase inhibitor is selective for phosphodiesterase type 5. The agent increases ocular nitric oxide levels through nitric oxide donors, stimulation of nitric oxide synthase or increase of the availability or longevity or nitric oxide.

Preferred composition: The opthalmic preparation comprises a carrier and **sildenafil citrate** at a concentration of 0.001 - 20 % weight per volume.

ABEX

ADMINISTRATION - The composition is administered to the eye, orally, in the form of an opthalmic preparation, topically or perenterally. The composition comprises a solution, gel, semisolid, suspension, metered dose

device, transdermal patch or film.
No dosages given.

EXAMPLE - A 63 year old man with dense pericentral visual field loss in the right eye and chronic excavatory optic **neuropathy** developed a new extension of his right inferiotemporal scotoma on Humphery 30-2 SITA-standard testing, splitting fixation with a threshold of 14 decibels in the macular zone of that quadrant. The patient had undergone over a dozen prior Humphrey field tests, showing perpetual progression of field loss despite maintaining intraoccular pressures (IOP) from 6-10 mmH without medication. Pericentral thresholds clockwise from superionasal were 26, 26, 14 and 25.
Shortly after performing visual field and contrast sensitivity testing the patient took a single 50 micro g oral dose of **sildenafil citrate** (**Viagra**), and repeated these visual test 110 minutes later. There was a dramatic resolution of the pericentral perimetric defect, which increased in threshold from 14-23 decibels. The clockwise progression of pericentral threshold values was 28, 29, 23, and 26 dB, a mean increase of 3.75 decibels for the macular region loci nearly a tenfold increase in light sensitivity.